Original Article
DOI: https://doi.org/10.4038/sjdem.v15i2.7524

Etomidate in the Treatment of Severe Cushing Syndrome: The Sri Lankan Experience

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Abstract

Background:
Severe Cushing syndrome is a medical emergency requiring immediate supportive and hypocortisolaemic therapy. Urgent treatment of hypercortisolaemia within 24 – 72 hours is recommended to prevent life-threatening complications. Etomidate is the only intravenous option and has the most rapid onset of action out of the drugs used in treating Cushing syndrome.

Methods:
We present a descriptive retrospective study of 9 patients with severe Cushing syndrome treated with Etomidate infusion at six different hospitals with Endocrine Units in Sri Lanka.

Results:
On analysis Etomidate used as first-line showed a drop of cortisol of 71%, a mean rate of reduction of cortisol of 104.3 nmol/l/hour, and a duration for cortisol to reach the desired level of 15 hours Low dose Etomidate infusion did not cause adrenal insufficiency irrespective of giving a bolus prior to infusion, but caused adrenal insufficiency only when the Etomidate infusion was commenced at a higher rate.

Conclusion:
We conclude that Etomidate is potentially a suitable first line treatment in severe Cushing syndrome, especially in a resource poor setting where other therapeutic agents are not accessible.

Keywords: Etomidate, Severe Cushing Syndrome, Cortisol, Cushing's drug treatment, Survival outcome

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Introduction

Severe Cushing Syndrome (SCS) is defined as elevated serum cortisol of more than 41 ug/dL (1100 nmol/L) at any time of the day, or a 24-h urinary free cortisol (UFC) more than fourfold the upper limit of normal and/or severe hypokalaemia (<3.0 mmol/L), along with the recent onset of one or more of the following: sepsis, opportunistic infection, intractable hypokalaemia, uncontrolled hypertension, oedema, heart failure, gastrointestinal haemorrhage, glucocorticoid-induced acute psychosis, progressive debilitating myopathy, thromboembolism or uncontrolled hyperglycaemia and ketoacidosis [1].

SCS is a medical emergency requiring immediate supportive and hypocortisolaemic therapy. This treatment should take precedence over establishing the underlying cause of Cushing syndrome (CS). Urgent treatment of hypercortisolaemia within 24 – 72 hours is recommended to prevent life-threatening complications [2]. The goal of medical therapy is to correct the metabolic derangements urgently, and to lower cortisol levels. If medical therapy fails to correct the severe metabolic derangements and hypercortisolemia, bilateral adrenalectomy can be lifesaving [2]. Surgery is the definitive therapy in CS, but medical therapy may be required in occult CS, while awaiting surgery, when surgery is contraindicated or unsuccessful, and while awaiting the effect of radiotherapy [3].

Steroidogenesis inhibitors play a major role in the management of severe CS irrespective of the pathological aetiology, with the broadest experience being with ketoconazole and metyrapone. Etomidate is the only intravenous therapeutic option, has the most rapid onset of action, and has several other benefits compared to other drugs used in CS, making it a beneficial medical therapeutic option in severe CS [4]. Adverse effects of etomidate given at non-hypnotic doses are uncommon [4]. The more recently introduced 11 beta-hydroxylase inhibitor, Olisodrostat, has been used effectively in severe CS, but the experience is limited [5].

Methodology

This is a descriptive retrospective analysis of nine patients with severe CS treated with an intravenous etomidate infusion. These patients were treated in six different hospitals in Sri Lanka, including three patients from the National Hospital of Sri Lanka, Colombo, two patients from Sri Jayewardenepura General Hospital, one patient from the National Hospital Kandy, one patient from the Teaching Hospital Karapitiya, Galle, one patient from the Teaching Hospital Kurunegala, and one patient from the Teaching Hospital Batticaloa. These patients were treated between the years 2016 and 2020, and were the only documented patients with severe CS treated with etomidate in the above hospitals during the data collection period.

Ethical approval was obtained from the Ethics Review Committee of the Sri Jayawardenepura General Hospital (SJGH/21/ERC/030). The patients comprised cases of severe CS treated with IV etomidate. Data was collected with regard to biographic details, details of the aetiology of CS, treatment, and response. Details were gathered from the patients' clinical records and were clarified by each patient's treating consultant endocrinologist. These details included if etomidate was used as first line, second line or third line, the regime of Etomidate dosage, and the cortisol response to treatment. Details of the prescribed etomidate preparation were gathered from the hospital pharmacists.

Results

The case series comprised 6 females and 3 males, while the mean ages of the two genders were 45.6 years and 36.3 years, respectively. The aetiology of 4 out of 9 patients was an ACTH-secreting pituitary microadenoma (cases 1,3,5,7). Two cases had primary bilateral macronodular adrenal hyperplasia (PBMAH) (cases 2,4). Two cases had ectopic ACTH secretion, including bronchial carcinoid with cyclical CS (case 8) and pheochromocytoma (case 9), respectively. Onepatient had right adrenocortical carcinoma (case 6). (Table 1) All patients had severe hypertension, diabetes, and proximal myopathy. 3 patients had altered mental status. 7 patients had infection, with 4 having severe sepsis, including severe pneumonia in 3 patients and fungal sepsis in 3 patients. (Table 1)

3 out of 9 patients were treated with etomidate as the first line therapy (cases 1,2,3). Etomidate was chosen in those cases as it was considered the preferred first line therapy in severe CS. All 3 patients recovered successfully, and neither of them developed adrenal insufficiency due to etomidate. These 3 cases comprised 2 ACTH secreting pituitary microadenomas. (cases 1,3)

and one BLMAH (case 2). The two other patients who recovered successfully were treated with etomidate as the second line after switching from fluconazole and itraconazole, respectively, following liver derangement and persistent hypercortisolaemia (cases 4,5). All those who were switched from ketoconazole to etomidate as the second line or third line succumbed to sepsis. Patient 6 was initially started on ketoconazole for antifungal cover and treatment of hypercortisolaemia, but was changed to etomidate due to poor response in cortisol reduction. Patient 8 was treated with etomidate following a failed response to both ketoconazole and metyrapone sequentially and because etomidate was the only IV option available in the intubated patient. However, this patient succumbed to sepsis. In case 9, etomidate was given as third-line treatment due to persistent hypercortisolaemia despite adrenalectomy for ACTH-secreting pheochromocytoma, but eventually succumbed to sepsis. (Table 2)

The mean percentage drop of cortisol from baseline in those treated with etomidate as first line, second line, and third line were 71% (range 65% - 78.6%), 62% (range 49.7% - 78.5%), and 40% (range 18.7% - 62.5%). The mean rate of reduction of cortisol was 104.3 nmol/l/hour (median 65.25 nmol/l/hour), when etomidate was used as the first line. The mean rates of cortisol reduction when etomidate was used as the second line and third were 29.9 nmol/l/hour

Table 1: Comparison of the clinical features and investigations of the 9 cases of severe CS

Case	Gender (M/F)	Age (years)	Diagnosis	HT	DM	Hypokalaemia	Alkalosis	Altered mental status	Sepsis	Myopathy	Dexamethasone suppression tests (nmol/L) and ACTH (7 – 63 pg/ml)	IPSS	Imaging
1	M	24	ACTH secreting pituitary microadenoma	√	√	√	√	Agitation	Pneumonia	√	ACTH 340	ACTH on the right and left sides 767 pg/ml and 353 pg/ml respectively, with increased central to peripheral ACTH ratio of the right and left sides of 2.36 and 1.08 respectively, indicating centralization, with a right to left lateralization index of 2.17 (>1.6) indicating lateralization to right	MRI - Right sided pituitary microadenoma measuring 0.6× 0.5× 0.5cm
2	F	56	B/L macronodular adrenal hyperplasia	√	√	√	√	-	Fungal nail infection	√	ACTH <10, ODST 566, LDDST 687, HDDST 598	All ACTH values less than 10 pg/ml	CECT - Bilateral hyperplastic adrenals
3	F	41	ACTH secreting pituitary microadenoma	√	√	-	-	-	-	√	ACTH 219, ODST 814, LDDST 749, HDDST 876	Increased central to peripheral prolactin adjusted ACTH ratio of the left and right side of 5.68 and 2.09 respectively, indicating centralization, with a left to right lateralization index of 1.6 (>1.6).	MRI – Pituitary appeared normal
4	F	38	B/L macronodular adrenal hyperplasia	√	√	√	√	Anxiety	Bacterial and fungal culture positive sepsis with infection in multiple sites	√	ACTH 1.6, ODST 789.9, LDDST 503.8		CECT – Bilateral macronodular adrenal hyperplasia
5	M	24	ACTH secreting pituitary microadenoma	√	√	√	-	-	-	√	ACTH 263, ODST 762, LDDST 356, HDDST 468	Basal central to peripheral ACTH ratios of 35.24 and 2.79 on the left and right sides respectively	MRI – Pituitary microadenoma
6	F	64	Right adrenocortical carcinoma	√	√	√	√	Confusion	Pneumonia, sepsis, type 2 respiratory failure, urinary infection	√	ACTH 17		CECT - Several masses in the right adrenal gland, with secondary deposits in regional lymph nodes, suggestive of adrenocortical carcinoma.
7	F	35	ACTH secreting pituitary microadenoma	√	√	√	√	Drowsiness	Candida septicaemia	√	ACTH 62	ACTH on the right and left sides 78 pg/ml and 90 pg/ml respectively, with increased central to peripheral ACTH ratio.	MRI – Pituitary microadenoma
8	M	61	Cyclical Cushing due to ACTH secreting bronchial carcinoid	√	√	√	√	-	Cavitatory pneumonia	√	ACTH 214 (normalised in between episodes), ODST 1004, LDDST 1450, HDDST 1400	Simultaneous bronchial and inferior petrosal sinus venous sampling showed very high ACTH levels at bronchial venous canulation sites.	CECT - Lingular lobe of the lung collapse and bilateral adrenal gland hyperplasia
9	F	40	Pheochromocytoma with ectopic ACTH secretion	√	√	√	√	-	Bronchopneumonia with candida sepsis	√	ACTH 278.8, ODST 893.9, LDDST 1230.5, HDDST 954.6		CECT - 7.7 ×7.9 × 8.2cm size heterogeneously enhancing left suprarenal mass, with baseline density more than 10 Hounsfield units, suggestive of a phaeochromocytoma

(M-male, F- female, HT – hypertension, DM – Diabetes Mellitus, ACTH – Adrenocorticotrophic hormone, B/L – bilateral, ACTH- Adrenocorticotrophic hormone, ODST – overnight dexamethasone suppression test, LDDST – low dose dexamethasone suppression test, HDDST – high dose dexamethasone suppression test, MRI – magnetic resonance imaging, CECT – Contrast-enhanced computed tomography, IPSS – inferior petrosal sinus sampling)

Table 2: Comparison of the treatment and outcome of the 9 cases of severe CS treated with IV etomidate

Case	1st line Rx	2nd line Rx	Subsequent Rx	Place of treatment with etomidate	Reason for etomidate	IV etomidate infusion rate	Baseline cortisol level (nmol/l)	Lowest cortisol level with etomidate (nmol/l)	Time taken for cortisol to reach the lowest level since commencement of etomidate (hours)	Rate of reduction of cortisol levels (nmol/l/hour)	Percentage drop of cortisol levels (%)	Duration of etomidate use (hours)	Side effects to etomidate or its formulation	Definitive Rx	Outcome
1	Etomidate		Hydrocortisone 100 mg/5 mg/5 mg following TSA	1st line	Preferred first line treatment for severe CS	0.03 mg/kg/hour	3456	983	11	224.8	71.5	24	N	TSA	Recovered
2	Etomidate			1st line	Preferred first line treatment in severe CS	0.03 mg/kg/hour (renal impairment)	858	300-400	24	23.25	65	168 (7 days)	N	Bilateral adrenalectomy	Recovered
3	Etomidate		Hydrocortisone 100 mg/5 mg/5 mg when serum cortisol dropped to 80 nmol/l in 2 days after hypophysectomy. This was tailed off in 4 months.	1st line	Preferred first line treatment in severe CS	0.04 mg/kg/hour	996	213 80 on post operative day 2	12	65.25	78.6	36	N	TSA	Recovered
4	Fluconazole	Etomidate	After IV hydrocortisone 100 mg at induction, a 100 mg/hour infusion was continued for 30 hours after ligation of adrenal arterie Hydrocortisone 100 mg/ 5 mg/ 5 mg Fludrocortisone 50 mg daily	2nd line	Liver enzyme derangement due to fluconazole and persistent hypercortisolaemia	0.3 mg/kg/hour 0.1 mg/kg/hour on day 3 0.02 mg/kg/hour on day 8	690	148 (day 3) Withheld on day 5 when cortisol dropped to 46. Restarted on day 8 when cortisol rose to 540 and then underwent adrenalectomy	72	7.53	78.5	120 (5 days)	Transient AI	Bilateral adrenalectomy	Recovered
5	Itraconazole	Etomidate	Hydrocortisone 100 mg/5 mg/5 mg following TSA	2nd line	Liver enzyme derangement due to itraconazole and persistent hypercortisolaemia	5 mg bolus followed by 0.03 mg/kg/hour	1393	700 192 on day 2 post-operatively, <50 nmol/l day 5 post- operatively	72	9.625	49.7	72 (3 days)	N	TSA	Recovered
6	Ketoconazole	Etomidate		2nd line	Severe hypercortisolemia not responding to ketoconazole	0.02 mg/kg/hour	10,000	3000	Patient died before cortisol levels could normalise	97.2	70	72 (3 days)	N	Died before planned adrenal debulking surgery	Died of sepsis, RF, DIC
7	Ketoconazole	Etomidate		2nd line	Poor response to ketoconazole	0.05 mg/kg/hour infusion	1000	500	96	5.2	50	216 (9 days)	N	Died before planned TSA	Died of Candida sepsis
8	Ketoconazole	Metyrapone	Etomidate	3rd line	Poor response to ketoconazole and metyrapone, and not tolerating oral drugs as the patient was intubated and ventilated	0.05 mg/kg/hr used intermittently titrated by serum cortisol values	1334	500	48	17.375	62.5	168 (7 days) block and replacement done with hydrocortisone when serum cortisol dropped to <400 nmol/l	N		Died of sepsis
9	Ketoconazole	Adrenalectomy	Etomidate Hydrocortisone 100 mg/5 mg/5 mg following adrenalectomy	3rd line	Post operative cortisol persistently high	0.03 mg/kg/hr increasing to 0.3 mg/kg/hour	1230	1000	48	4.8	18.7	72 (3 days)	N	Unilateral adrenalectomy	Died of sepsis

Rx- treatment, IV – intravenous, CS – cushing syndrome, N – none, AI – adrenal insufficiency, TSA – trans-sphenoidal adenectomy, RF, renal failure, DIC – disseminated intravascular coagulation

(median 8.58 nmol/l/hour) and 11 nmol/l/hour (median 11.9 nmol/l/hour), respectively. The mean time taken for cortisol to reach the lowest level was 15 hours when etomidate was used as the first line, and was 80 and 48 hours when etomidate was used as 2nd line and 3rd line respectively. (Table 2)

The patients took an average of 48 hours to reach the lowest achieved cortisol levels since starting the etomidate infusion, excluding the patient with ACC (case 6), who died before the desired cortisol level was achieved. Those who recovered successfully took a mean duration of 38.2 hours.(median 24 hours, range 11 – 72 hours) of etomidate infusion to reach target cortisol levels, and was continued for a mean of 84 hours (median 72 hours, range 1 – 7 days) (cases 1,2,3,4,5). The mean total duration of continuing etomidate infusion was 105.3 hours (median 72 hours, range 24 – 216 hours). (Table 2)

The patient with cyclical CS (case 8) was treated with block and replacement regime with etomidate, while in other cases, the etomidate dose was titrated according to cortisol levels. Only 1 patient (case 4) developed adrenal insufficiency due to etomidate. In this case etomidate infusion was started with a high dose of 0.3mg/kg/hour instead of the standard low dose infusion rate. All other patients were started with standard low dose etomidate infusion, and were gradually titrated according to the response, and none of them developed adrenal insufficiency (AI). Only one patient (case 5) was given a prior etomidate IV bolus, and recovered successfully, becoming normocortisolaemic in 72 hours, without adrenal insufficiency. None of the patients developed any other side effects to etomidate or its formulation. All patients were treated with Etomidate-Lipuro (lipid formulation). All patients were carefully monitored by expert teams during treatment with cortisol measurements done every 4 to 8 hours. Seven patients were treated in the Intensive care unit (ICU0 (cases 1,3,4,5,6,7,8) and 2 were treated in the High dependency unit (HDU) (cases 2,9).

Discussion

To our knowledge, there are only a few reported case series and case studies of severe CS treated with etomidate; a study of 14 cases by Constantinescu et al. in 2020, a series of 3 cases by Łebek-Szatańska et al. in 2019, a study of 7 cases by Carroll et al. in 2018, a series of 6 cases by Schulte et al. in 1990, and a series of 6 cases by Allolio et al. in 1988 [6][7][8][9][10]. In light of this, we report a series of 9 severe CS patients who were treated with etomidate.

Etomidate is an imidazole derivative that blocks multiple steps of steroidogenesis including side chain cleavage enzyme, 11β-hydroxylase, 17αhydroxylase, and aldosterone synthase [11]. Etomidate has shown antiproliferative and anti-tumorigenic effects on adrenocortical cells, which may be effective for the treatment of adrenocortical adenomas and metastatic adrenocortical carcinomas [11]. Etomidate has been effective in cases resistant to ketoconazole, and is also used as a therapeutic alternative in cases of transaminitis due to ketoconazole, which was evident in this case series [13].

Etomidate shows a dose dependant decrease of serum cortisol rapidly after administration, with levels falling 12 to 24 hours later [14]. A recent validation of a standard protocol for etomidate infusion in treating severe CS was introduced by Carroll et al. in 2019 based on a study of 7 cases treated with etomidate [8]. They recommended an initial bolus dose of 5 mg IV once over 2 -3 minutes, followed by an infusion rate of 0.02 mg/kg/h given via central line, titrated every 6 hours by 0.01 or 0.02 mg/kg/h increments to a maximum rate of 0.3 mg/kg/h [8]. They showed a median of 38 hours ranging from 26 to 134 hours to achieve a median nadir serum cortisol of 15.8 µg/dL (435 nmol/L) [8]. Similarly, in our study, those who recovered successfully took a mean of 38.4 hours [median 24 hours], ranging from 11 to 72 hours since starting etomidate infusion to reach target cortisol levels. Carroll et al. showed a median cortisol reduction rate of 1.09 µg/dL/h [30 nmol/l/hour] (range, 0.78 to 4.97 µg/dL/h [21.5 – 137 nmol/l/hour]) with etomidate [8]. The cortisol reduction rate of 104 nmol/l/hour seen in our study is comparable to the range of 21.5 – 137 nmol/l demonstrated by Caroll et al. The median reduction in cortisol of 80% (range, 67% to 95%) demonstrated by Caroll et al. was slightly higher than the 71% reduction we demonstrated when etomidate was used as 1st line treatment [8].

Drake et al. and *Krakoff et al.* reported prolonged use of etomidate infusion both for severe CS due to ectopic ACTH-secreting pancreatic tumours used for 8 weeks and 5.5 months, respectively [15][16]. *Drake et al.* completely blocked and replaced cortisol [15]. *Krakoff et al.* partially blocked cortisol, but the patient developed adrenal insufficiency persisting up to 14 days after omitting etomidate, and had no other major side effects other than transient myoclonus [16]. Other reported cases have shown AI for 24 hours to 4 days following cessation of etomidate [17]. This prolonged effect of etomidate after its cessation was explained as re-equilibration of this lipophilic drug to the plasma compartment from the adipose tissue storage [16]. *Łebek-Szatańska et al.* continued the lipid formulation of etomidate for 58 days, successfully treating CS, without developing AI or any other side effects [7]. However, AI was commoner in combination therapy with ketoconazole and metyrapone seen in 15% of cases compared to etomidate [18]. The duration of continuation of IV etomidate in our series ranged from 1 to 9 days, and the extended duration of etomidate was not associated with AI. The evidence regarding the safety of continuing etomidate infusion for more than 2 weeks is limited and is thus currently recommended safe for use for no longer than 7 to 10 days, according to *Caroll et al.* [8].

Constantinescu et al. compared the outcome of low-dose and high-dose etomidate use in treating severe CS [6]. The low-dose group started with an etomidate infusion rate of 0.02 – 0.04 mg/kg/hour rate of etomidate, and the high-dose group started with 0.1 – 0.3 mg/kg/hour rate. The low-dose group took 3 days to reach the target cortisol level of <500 nmol/l, whereas the high-dose group took only 1 day [6]. However, all those in the high-dose group developed drowsiness and AI, while the low-dose

group developed no such adverse effects [6]. One patient in our series was commenced on a high dose rate of etomidate infusion, and was the only patient who developed unwanted AI. However, this was reversible, and there was no significant reduction in the duration of the etomidate requirement.

During treatment with etomidate, the risk of AI was commoner in ACTH-independent CS, than in ACTH-dependent CS, the postulated mechanism being high ACTH levels increasing the synthesis of other steroid hormones. Therefore, ACTH dependent CS may require higher etomidate doses [14]. The Endocrine Society suggests that etomidate infusion rate can be titrated to achieve a stable serum cortisol level between 10 – 20 ug/dL (280 – 560 nmol/L), or a "block and replacement" strategy can be used [4]. The block and replacement strategy was preferred in cyclical CS, as in patient 8, in order to avoid frequent dose adjustments [14]. However, this method may have a higher risk of side effects due to the higher doses of etomidate required [7]. Reduced etomidate dosing is recommended in the elderly, critically ill, and in those with renal impairment due to reduced protein binding [8][16]. Etomidate, if given at high doses for sedation, may cause nausea (<10%), vomiting (10%) and myoclonus (33%), and may very rarely cause haemodynamic instability [8].

Higher dose regimes can cause side effects due to the solubilizing agent propylene-glycol including thrombophlebitis, pain in the injection site, haemolysis, nephrotoxicity due to proximal renal tubular injury and lactic acidosis [8].A lipid formulation of IV etomidate (Etomidate Lipuro) is a therapeutic alternative that exerts the same cortisol lowering effects, but has lower rates of propylene-glycol related side effects [8]. Therefore, Etomidate Lipuro is safe to be given via a peripheral line unlike the propylene glycol preparation which needs central line administration [19].

The patient with ACC (case 6) in our study had a baseline and lowest level of cortisol more than 10,000 nmol/l in dilution, and 3000 nmol/l, respectively, where the definite value could be much higher. However, this significantly high cortisol value could be due to assay interference with cortisol precursors in ACC which could not be tested separately with standard cortisol immunoassays, highlighting the importance of utilizing mass spectrometry to overcome this challenge [20]. The inability to quantify this patient's actual serum cortisol level was a limitation in our study.

Close monitoring of the haemodynamic status, possibility of AI, level of consciousness, electrolytes and cortisol levels is required every 4 to 8 hours during treatment with etomidate. Though some experts recommend ICU or HDU care during treatment with etomidate, *Constantinescu et al.* showed no significant difference in outcome in those managed in the ICU and non-ICU setting [6]. Therefore, unless patients with severe CS are intubated and ventilated or require organ support, they can be successfully and safely managed in the non-ICU setting, provided the staff is skilled in close monitoring [6][21]. *Soh et al.* established a protocol for the safe treatment of CS with etomidate in the general medical ward [19]. This protocol excludes the mandatory requirement of an ICU bed as a limiting factor in using etomidate in the treatment of severe CS. Etomidate is also a cost-effective treatment option, considering the fact that the cost of treatment in ICU may not be required. Considering the wide range of benefits of etomidate in treating severe CS, it is not necessary to defer treatment with etomidate due to the unavailability of ICU beds. Etomidate being an anaesthetic drug, is widely available even in a resource poor setting such as ours, illustrating the ability to utilize this agent in a wide array of clinical situations.

A limitation of this study is that it consisted of only 9 patients, and therefore the statistically significant power of the findings may be limited. However, this was an important population as they were the only patients with SCS who were treated with Etomidate in Sri Lanka to date. Etomidate was used in these patients for the treatment of SCS and as it was an easily available cost-effective drug option in a resource poor setting. However, the pathological aetiology and severity of CS varied among these patients. This variation may have been a confounding factor to the outcomes in addition to the effect of Etomidate itself. Since patients who failed other prior treatment options were started on Etomidate as the second or third line agent, there is a possibility these patients were more treatment resistant. This would erroneously suggest a poor response in patients who were treated with etomidate as the second or third line agent. This is another limitation in this study being a retrospective observational study. Further more extensive studies are warranted to assess the place of Etomidate in treating SCS.

Conclusion

Etomidate used as first-line therapy in treating SCS has good efficacy in reducing cortisol to desired levels, and improves overall survival outcome. Etomidate use in treating SCS is unlikely to cause AI unless initiated as a high dose rate of infusion. Thus, low dose etomidate infusion with or without prior bolus is considered safe and effective. We recommend etomidate as a potential first-line treatment in SCS especially in resource poor settings where other therapeutic agents are not available.

Abbreviations:

CS	Cushing syndrome
SCS	Severe cushing syndrome
ACTH	Adrenocorticotrophic hormone
IV	Intravenous
AI	Adrenal insufficiency
SJGH	Sri Jayewardenepura General Hospital
ICU	Intensive care unit
HDU	High dependency unit
BLMAH	Bilateral macronodular adrenal hyperplasia
ACC	Adrenocortical carcinoma
TSA	Trans-sphenoidal adenectomy

Declarations:

Ethics approval and consent to participate: Ethical approval was obtained from the Ethics Review Committee of the Sri Jayawardenepura General Hospital (SJGH/21/ERC/030), and informed consent was received from patients of whom data was collected retrospectively for the study and publication. All methods were carried out in accordance with relevant guidelines and regulations of the relevant Ethics review committee.

Competing interests: There are no competing interests.

Funding: No funding was received for this study

Authors' contributions: The patients in this study were treated by Consultant Endocrinologists DM, KL, SP, MS, DK, SC, CA, MW, NS, CS. Data collection, analysis and writing up of the manuscript was done by Senior Registrar in Endocrinology KPJ under the supervision of DM. The final manuscript was read and approved by all authors DM, KPJ, KL, SP, MS, DK, SC, CA, MW, NS, CS.

Acknowledgements: We are grateful to the patients who consented to allow their treatment data to be used in the study, and the healthcare staff involved in treating these patients.

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