Observational Study

Medicine®

OPEN

Comparing the utility of 30- and 60-minute cortisol levels after the standard short synacthen test to determine adrenal insufficiency

A retrospective cross-sectional study

Muhammad Imran Butt, MBBS, FHEA, FRCP, FACE[a,b,*], Nouf Alzuhayri, BSc[a], Lama Amer, MBBS[a], Muhammad Riazuddin, MBBS, FRCP[a,b], Hadeel Aljamei, MBBS[a], Muhammad Sohaib Khan, MBBS, FCPS[a], Mohammed Abufarhaneh, MBBS[a], Eman Alrajhi, MBBS[a], Anhar Alnassar, MBBS[a], Reem Alahmed, BSc[a], Dina Mahmoud Ahmad Aljayar, MBBS[b], Fayha Farraj Abothenain, MBBS[b], Edward De Vol, PhD[a]

Abstract

Short Synacthen test (SST) involves measuring the baseline, 30-, and 60-minute serum cortisol levels, after injecting 250 μg of synthetic adrenocorticotropic hormone or Synacthen (ACTH). This study aimed to review the current clinical practice of performing SST to establish a standardized test protocol and to additionally test the hypothesis regarding performing the 60-minute cortisol test alone and the dependence of overall SST result on baseline cortisol level.

Patients >14 years who underwent SST from January 2010 to December 2017 were included. Pearson's chi-square cross-tabulation was used to identify individuals with inconsistent 30- and 60-minute serum cortisol test results. Logistic regression analysis was performed to predict normal responses based on the baseline cortisol value.

Of the 965 patients identified from pharmacy, medical, and laboratory records, 849 were included. Mean baseline, 30-, and 60-minute cortisol levels after ACTH injection were 394 ± 286.58, 722 ± 327.11, and 827 ± 369.30 nmol/L, respectively. Overall, 715 (84%) and 134 (16%) patients had normal and abnormal responses, respectively. Primary and secondary adrenal insufficiency was diagnosed in 10% and 35%, respectively, while ACTH levels were not measured in 55% of the patients. Overall, 9.49% (n = 72) of the patients had a suboptimal response at 30 minutes, but reached the threshold value of 550 nmol/L at 60 minutes. This particular subgroup's mean change (240 nmol/L) in cortisol level from baseline to 30-minute was higher than that observed in patients with abnormal response at both time-points (mean change, 152 nmol/L). No patient with 30-minute optimal responses had 60-minute suboptimal responses. The baseline serum cortisol threshold of ≥226 nmol/L had 80% sensitivity, 71% specificity, and 93% positive predictive value for detecting a normal SST (*P*-value < .0001).

Relying on a 60-minute cortisol level can identify all normal and abnormal responses, while relying on 30-minute cortisol level alone may produce false-positives. Additionally, a baseline cortisol level of ≥226 nmol/L is a reliable threshold for determining adequate adrenal function, particularly with a low pretest hypoadrenalism probability.

Abbreviations: ACTH = adrenocorticotropic hormone, ANOVA = analysis of variance, HPA = hypothalamic-pituitary-adrenal, ITT = insulin tolerance test, SST = short Synacthen test.

Keywords: addison disease, adrenal insufficiency, adrenocorticotropic hormone, cosyntropin, hypothalamicpituitary-adrenal axis, pituitary-adrenal system

Editor: Undurti N. Das.

The authors have no conflicts of interest to disclose.

There was no funding involved in performing this study.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

[a] King Faisal Specialist Hospital & Research Centre, Zahrawi St, Al Maather, [b] Al Faisal University, Al Zahrawi Street, Riyadh, Kingdom of Saudi Arabia.

[*] Correspondence: Muhammad Imran Butt, Consultant Endocrinologist, King Faisal Specialist Hospital & Research Centre & Al Faisal University, Riyadh, MBC 46. Kingdom of Saudi Arabia, Postal code 11211 (e-mail: mimran74@hotmail.com).

How to cite this article: Butt MI, Alzuhayri N, Amer L, Riazuddin M, Aljamei H, Khan MS, Abufarhaneh M, Alrajhi E, Alnassar A, Alahmed R, Aljayar DM, Abothenain FF, De Vol E. Comparing the utility of 30- and 60-minute cortisol levels after the standard short synacthen test to determine adrenal insufficiency: A retrospective cross-sectional study. Medicine 2020;99:43(e22621).

Received: 1 January 2020 / Received in final form: 2 April 2020 / Accepted: 8 September 2020

http://dx.doi.org/10.1097/MD.0000000000022621

1. Introduction

The insulin tolerance test (ITT) has been historically been used for evaluating the integrity of the hypothalamic-pituitary-adrenal (HPA) axis. Although both the ITT and short Synacthen test (SST) are useful in detecting secondary adrenal insufficiency, ITT is labor intensive and requires medical and nursing supervision. Performing this in children and patients with seizures, cardiovascular, and cerebrovascular diseases also has its limitations.

Plumpton and Besser investigated the cortisol response to hypoglycemia by undertaking ITT in healthy individuals; they showed that the maximum response ranged from 21 to 48 μg/dL and therefore proposed 20 μg/dL (550 nmol/L) as the minimum threshold level for a normal cortisol response to insulin-induced hypoglycemia.[1] They used an immunofluorescent assay, which measures cortisol and corticosterone levels and therefore has a 20% to 30% positive bias. Carr et al later compared radioimmunoassay (RIA) with immunometric assays. In 154 basal and stimulated serum cortisol samples, they observed that the mean result obtained with an RIA was 23% lower than those obtained with an immunometric assay.[2] They observed a similar correlation in the results of patients who underwent either a short Synacthen test (SST) or ITT. Moore et al compared different assays for cortisol, and observed lower cortisol levels with RIA.[3]

Cho et al. investigated[4] over 200 healthy individuals to define the normal thresholds for serum cortisol levels upon stimulation in dynamic studies; however, they used an RIA instead of the traditional fluorometric assay, used in earlier studies.[1] Following an ITT, the 95th percentile of the peak serum cortisol was 15 μg/dL (414 nmol/L), which was proposed to be the reference level for healthy volunteers. The study participants also underwent either a low dose (1 μg) or standard dose (250 μg) SST. All those who underwent the low dose SST had serum cortisol level >18 μg/dL (497 nmol/L) while those who underwent the standard-dose SST had serum cortisol ≥20 μg/dL (550 nmol/L). The use of this threshold as the standard dose SST was therefore suggested.[4] They also measured cortisol levels with 2 different RIAs and found that the results correlated with each other.

The reliance on the 30-minute serum cortisol value stems from studies done with ITT and how it relates to serum cortisol levels attainted 30 minutes after an adrenocorticotrophic hormone (ACTH) injection.[5] However, Dorin et al showed that ACTH concentration remains well above the threshold for maximal cortisol secretion for up to 2 hours following cortisol sampling, after IV SST. He showed that serum cortisol continues to rise and peaks 60 minutes after the ACTH injection in normal healthy adults. This provides a rationale for measuring 60-minute serum cortisol rather than just up to 30 minutes in patients who undergo SST.[6] Alia et al studied the profile of serum cortisol in 10 healthy volunteers after the low and standard doses SST with at least 1 week between each test; they observed that cortisol continues to rise, reaching a peak after 30 minutes irrespective of the ACTH dose.[7] Longui et al drew a similar conclusion when they examined 64 healthy adults with a standard dose SST and determined that peak serum cortisol was attained, 60 minutes after the injection.[8]

Clinicians have been using SST with increasing frequency because of its ease; it is now replacing ITT for the assessment of adrenal reserve. Approximately 50% of surveyed clinicians were using SST to assess the HPA axis in 1996, which was in sharp contrast to only 25% in 1988.[5,9] SST provides an excellent clinical tool to test the HPA axis and has several advantages including relative ease and simplicity, lower cost, and accurate assessment of cortisol secretion. However, a wide variation occurs with the time points used for measuring cortisol levels after ACTH injection. For instance, some clinicians use the 30- and 60-minute serum cortisol level measurements, while some prefer either the 30-minute or the 60-minute serum cortisol measurements alone. Further, some clinicians measure the baseline serum cortisol before ACTH injection while others omit it.

At our institution, we measure the serum ACTH levels before ACTH administration. This later helps to differentiate between primary and secondary adrenal insufficiency in those who show insufficient cortisol response. The objective of this study was to determine the current clinical practice involved in performing SST and to establish a standardized test protocol.

2. Objectives

In this retrospective analysis we determined the following:

(1) False positive diagnosis of adrenal insufficiency: We clarified if in a situation a false positive diagnosis of adrenal insufficiency could have been reported based on the 30-minute serum cortisol level, but with a normal 60-minute level. We also clarified another false positive situation in which only the 60-minute test was done and was below the threshold, but the patients could have had a normal result at 30 minutes if it had been checked.
(2) Setting the baseline cortisol threshold: We clarified the correlation between the baseline cortisol level and the final SST results.

3. Methods

In accordance with the STROBE guidelines, we performed a retrospective cross-sectional review of data of all patients who underwent SST from January 2010 to December 2017 at our institution. We used a cut off age of 14 years (considered adulthood in the region) and identified eligible patients using the hospital electronic clinical documentation, laboratory, and prescription records.

We excluded patients who underwent pituitary surgery in the preceding 2 months, those who received exogenous steroids and opioids for 2 weeks prior to undergoing the test, and those on oral contraceptives. Patients underwent most of the tests in the outpatient clinic setting, medical day units, and during hospitalization, under nursing supervision. All patients received Cosyntropin 250 μg, a synthetic ACTH1–24 (Amphastar pharma), either via the intravenous or intramuscular route. We anonymized and collected the data in the Research Electronic Data Capture software hosted and archived at our institution; these data are available for any future reference. We used Roche Elecsys 2010 modular analytics with an electrochemiluminescence immunoassay (Roche diagnostics, Switzerland) for serum cortisol measurement. The coefficient of variation for the analyzer was 1.7%. The cortisol assay had recovery results from 89% to 111%. The assay was unaffected by icterus (bilirubin <60 mg/dL or <1.026 mmol/L), anemia (Hb < 1.2 mmol/L or <1.9 g/dL), and Biotin (<123 nmol/L or <30 ng/mL).

We conducted the study following the guidelines outlined in the declaration of Helsinki. This study was approved by the Institutional Ethics Committee of King Faisal Specialist Hospital

& Research Centre and a waiver for the need for informed consent was granted.

3.1. Local SST protocol and interpretation

As our study was a retrospective analysis, we collected data on all protocols adopted by the clinicians. We defined a normal response as a stimulated cortisol value ≥550 nmol/L achieved at 30 or 60 minutes or at both time points. An abnormal response referred to a stimulated cortisol value <550 nmol/L. Primary adrenal insufficiency was defined when the patient had an inadequate response (ie, cortisol <550 nmol/L with corresponding elevated ACTH levels when ACTH results were available). Secondary adrenal insufficiency was defined by an inadequate response (ie, cortisol <550 nmol/L with corresponding low ACTH levels when ACTH results were available).

3.2. Statistical analysis

We performed statistical analysis using JMP Pro 14 software version 11.1.1 (SAS Institute, Cary, North Carolina). We used descriptive statistics for categorical variables, reported as frequency and percentages. For continuous variables, we used mean values and standard deviations. Pearson's Chi-square cross-tabulation was used to identify individuals who had inconsistent serum cortisol results at 30 and 60 minutes. We considered an alpha level of 0.05 as the point indicating a significant statistical difference. We used logistic regression analysis to predict a normal response based on the baseline cortisol value. Additionally, we performed a receiver operating characteristic (ROC) curve analysis to estimate the threshold baseline value that would predict the outcome status. We determined the threshold value that was associated with the maximum sensitivity and subtracted (1-specificity). Analysis of variance (ANOVA) was used to compare the mean cortisol change (30 minutes minus basal cortisol) between 3 groups identified based on the SST result. We performed a Tukey-Kramer analysis as a post-hoc test.

4. Results

We identified 965 patients from the prescription, medical, and laboratory electronic records at the hospital. We excluded 116 patients who did not meet our inclusion criteria and included 849 patients in the analysis. We summarized the baseline demographics of the study population in Table 1. In most cases, clinicians did not document the reason for performing the test. The mean age of patients was 50.5 ± 20.45 years, mean weight was 67 ± 21 kg, the mean body mass index was 26 ± 7.74, and 54% of patients were female.

Measurements for the baseline, 30-, and 60-minute serum cortisol levels alone were available for 846, 784, and 848 patients, respectively. In 759 patients, the 30- and 60-minute serum cortisol measurements were available. In 741 patients, the baseline, 30-, and 60-minute cortisol measurements were available, and these 741 patients' data were used in the ROC as they had baseline cortisol values; furthermore, we also used their data in ANOVA where 30 minus baseline change was reported. The baseline ACTH level was measured in 231 patients (Fig. 1). The mean baseline, 30-, and 60-minute cortisol values after ACTH injection were 394 ± 286.58 nmol/L, 722 ± 327.11 nmol/L, and 827 ± 369.30 nmol/L, respectively. Overall, 715 patients out of 849 (84%) had a normal response while 134 patients out of 849 (16%) had an abnormal response. The diagnosis of primary and secondary adrenal insufficiency was made in 10% and 35% of patients, respectively. The ACTH levels were not measured in 55% of the patients and therefore, they could not be classified as having either primary or secondary adrenal insufficiency (Fig. 2).

Table 1

Baseline characteristics of all patients (n = 873)*.

Age (yr), mean ± SD	50 ± 20
Gender	
Male n (%)	402 (46.05%)
Female n (%)	471 (53.95%)
Body mass index (Kg/m^2), mean ± SD	26 ± 7.74
Indications for performing SST n (%)	
Unknown	549 (62.88%)
Hyponatremia	144 (16.49%)
Hypotension	82 (9.39%)
Visual field deficit	27 (3%)
Hypoglycemia	22 (2.5%)
Multiple indications	28 (3.2%)
Others	21 (2.54%)
Route of ACTH n (%)	
Intravenous (IV)	839 (96%)
Intramuscular (IM)	23 (3%)
Unknown	11 (1%)

ACTH = adrenocorticotropic hormone, IM = intramuscular, IV = intravenous , SD = standard deviation, SST = short synacthen test.

* 24 patients had morning serum cortisol and ACTH injection but did not stay for completion of test.

Figure 3 shows the cross-tabulation of SST results for 759 patients who had available measurements for both the 30- and 60-minute serum cortisol. Overall, 553 (72.85%) patients showed normal responses at 30 and 60 minutes (Group A); 134 (17.66%) patients showed abnormal response at both time points (Group B); 72 patients (9.49%) had an inadequate response at 30 minutes but a normal response at 60 minutes to pass the test (Group C). We did not have any patient who passed at 30 minutes and later fail at 60 minutes.

Logistic regression analysis showed that baseline serum cortisol had significant relationship with SST results ($P < .0001$) (Table 2). Therefore, ROC curve analysis was performed to estimate the specificity and sensitivity of the baseline cortisol test to predict the SST result (Fig. 4). As shown in Table 3, we identified the highest sensitivity and specificity and reported it as a pooled value (0.5093). This was associated with the baseline cortisol level of 226 nmol/L (as a threshold), and showed 80% sensitivity, 71% specificity, and 93% positive predictive value for detecting patients who would pass the SST.

Table 4 shows the mean change in cortisol level from baseline to 30-minute post ACTH injection among the 3 groups of patients as shown in the cross-tabulation (Fig. 3). Group A had the highest change between 0 to 30 minutes, with a mean (standard deviation [SD]) of 378 ± 214 nmol/L. We observed the lowest cortisol change in Group B, with a mean (SD) of 152 ± 113 nmol/L, while a mean (SD) cortisol change of 240 ± 145 nmol/L was observed in Group C. ANOVA was significant with an F value of 78.44, $P < .0001$. (Table 5)

We performed a Tukey-Kramer post-hoc test to assess the differences across groups. All groups differed from one another with the highest difference observed between groups A and B,

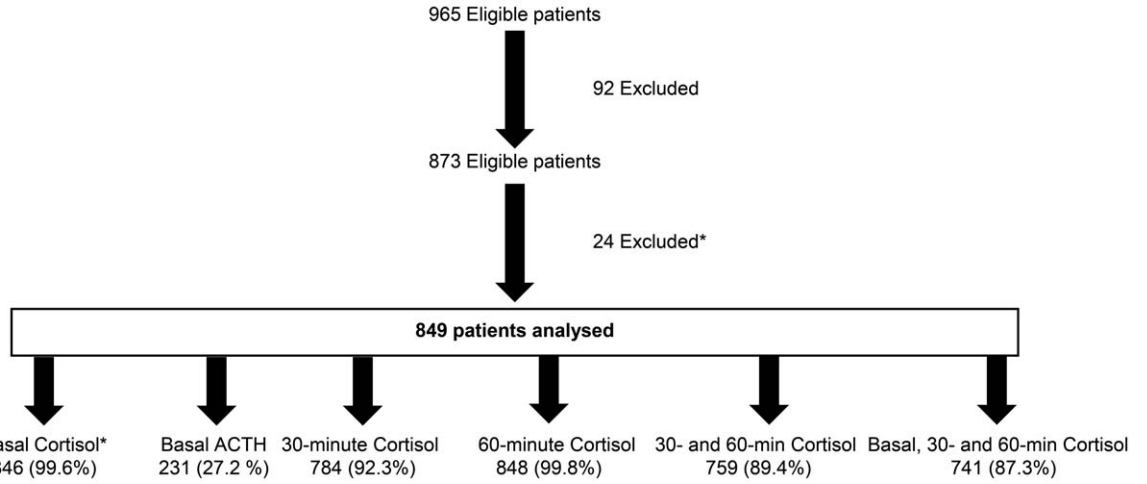

Figure 1. Study design and results. *24 patients had morning serum cortisol and ACTH injections but did not stay for completion of test. ACTH = adrenocorticotropic hormone.

with the difference being 225.77 nmol/L [95% confidence interval: 181.24, 270.30]; $P < .0001$. (Table 6).

5. Discussion

Our results showed that in many patients with low pretest probability, baseline serum cortisol can be used as a screening tool to further triage patients and determine those that require SST. The high predictive value of the baseline serum cortisol level confirmed in our study is natural based on the response of high-speed ACTH to stress. The threshold of 226 nmol/L identified in this study is similar to that described by other investigators.[10–12] Yip et al reported that a threshold of 266 nmol/L can be used to identify all patients who would have a successful SST outcome.[10] Likewise, Watts et al who measured morning serum cortisol 3 days after pituitary surgery and performed ITT in patients found that all patients with normal ITT had a morning cortisol level of ≥250 nmol/L. All these patients underwent standard dose SST a month after surgery to detect any delayed HPA axis irregularity; however, all patients were found to have normal SST.[11] A recent meta-analysis of 13 studies reported a much higher cortisol threshold of ≥365 nmol/L for normal SST.[12] These variations might be due to different cortisol assays used in the studies, samples obtained at different times of the day (early morning vs late morning) and variations in pituitary surgical history among the patients. Despite these variations, we recommend checking baseline cortisol level and if it is robust, it negates the need for a full SST.

In almost all cases in our study, clinicians reviewed the baseline cortisol level obtained on the day of the SST after the entire SST results were available. This made the use of the baseline cortisol measurement performed on the day of the test questionable. However, as a standalone screening test to identify patients at risk, it will have a more discriminatory role, and might reduce the need for performing SST unnecessarily in those with a robust baseline cortisol level.

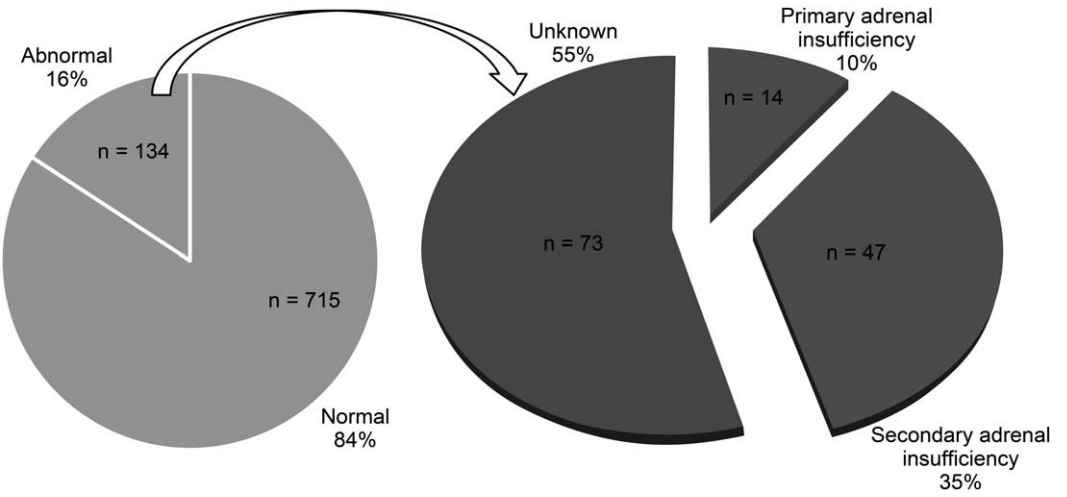

Figure 2. Results of SST. SST = short Synacthen test.

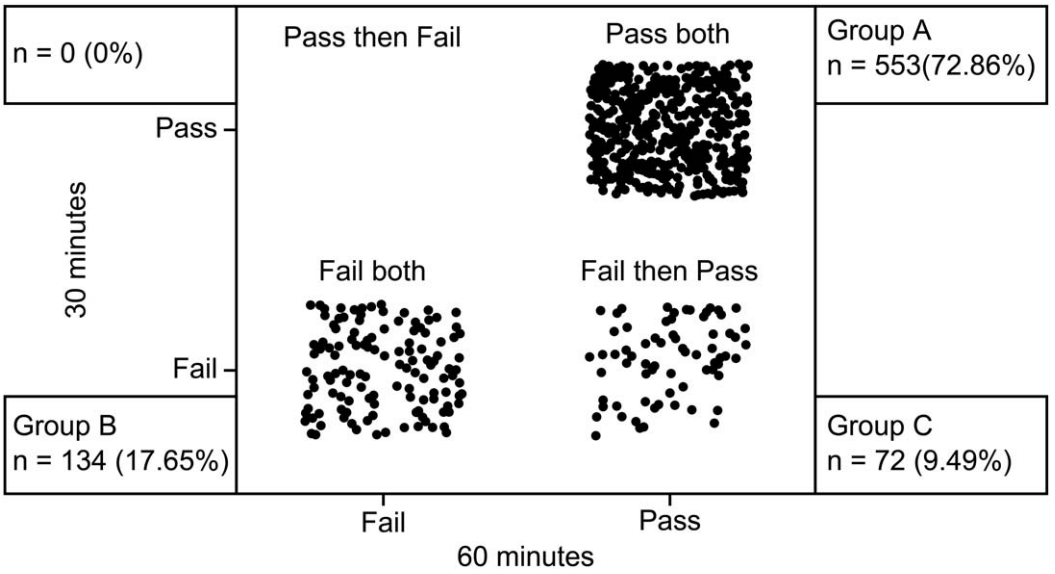

Figure 3. A scatterplot displaying the relationship between 30 and 60-minute serum cortisol values after ACTH injection and the final result of SST. ACTH = adrenocorticotropic hormone, SST = short Synacthen test.

Table 2

Logistic regression analysis of association between basal cortisol values (normal or abnormal) and SST results.

Term	Estimate	Std Error	Chi-square	Prob>ChiSq
Intercept	0.77367003	0.2110683	13.44	0.0002
Basal Cortisol	−0.0091718	0.0009123	101.07	<.0001

Chisq = Chi square, SST = short synacthen test, Std = standard.

Many studies have reported peak cortisol levels beyond 30 minutes following ACTH in patients suspected of hypoadrenalism (See Table 7).[13–16] Consistent with this, our results also showed that a single serum cortisol value obtained at 60 minutes after the ACTH injection is reliable for identifying all patients with normal or abnormal HPA axis. Reliance on a single 30-minute serum cortisol level would lead to significant false-positive results and unnecessary lifelong treatment, putting patients at risk for conditions such as diabetes, hypertension, and dyslipidemia. Therefore, we recommend serum cortisol measurements 60 minutes from ACTH injection as a reliable to assess the adequacy of cortisol secretion.

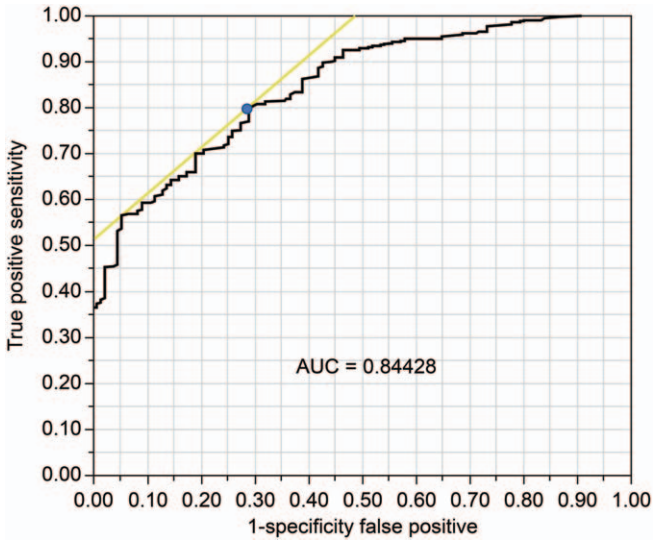

Figure 4. Receiver operating characteristic curve for basal cortisol and overall result of SST. AUC = area under the characteristics curve, SST = short Synacthen test.

In the present study, most clinicians obtained baseline serum cortisol levels followed by 30- and 60-minute serum cortisol levels after ACTH injection; however, based on our results and earlier studies we question the value of 30-minute cortisol level attained in the standard-dose SST. There is a very subtle risk of diagnosing a patient with hypoadrenalism if 30-minute serum cortisol assessments are avoided (when the result is suboptimal at 60 minutes but normal at 30 minutes); however, in such borderline cases, clinicians often repeat the test[13,15] although guidelines still recommend it when investigating for primary adrenal insufficiency.[17]

Our results show that only a quarter of the patients had a baseline ACTH level assessment. The missing patient information is of significant value as patients with diagnosed central hypoadrenalism would need further assessment for other pituitary hormone deficiencies and may need more in-depth pituitary imaging. There are therapeutic implications for these patients as well as in secondary hypoadrenalism; glucocorticoid replacement may suffice because of the intact renin-angiotensin-aldosterone system.

It remains unclear why no records were kept for a majority of our patients on the indications for performing the test in the

Table 3

Basal cortisol ROC analysis.

X	Prob	1-Specificity	Sensitivity	Sens-(1-Spec)	True Pos	True Neg	False Pos	False Neg
226.00	0.7857	0.2901	0.7994	0.5093*	554	93	38	139

Neg = negative, Pos = positive, Prob = probability, ROC = receiver operating characteristic, Sens = sensitivity, Spec = specificity.

Table 4

One-way ANOVA showing the mean cortisol change from time 0 to 30 minutes.

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Group A	538	378.104	8.390	361.63	394.58
Group B	131	152.333	17.004	118.95	185.71
Group C	72	240.042	22.936	195.01	285.07

ANOVA = analysis of variance, Std = standard.

Table 5

Analysis of variance (ANOVA) showing cortisol change from time 0 to 30 minutes.

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
A, B, and C groups	2	5942464	2971232	78.4482	<0.0001
Error	738	27951803	37875		
C. Total	740	33894267			

DF = degree of freedom, Prob = probability.

Table 6

Tukey Kramer analysis for pairwise group comparisons of cortisol change from time 0 to 30 minutes.

Group	Comparison group	Difference between the 2 groups	Std Err Dif	Lower CL	Upper CL	*P*-Value
Group A	Group B	225.7713	18.96108	181.2422	270.3004	<.0001
Group A	Group C	138.0624	24.42217	80.7082	195.4166	<.0001
Group C	Group B	87.7088	28.55110	20.6581	154.7596	.0062

CL = confidence level, Std Err Dif = standard error of difference.

Table 7

Studies reporting 30- and 60-minute serum cortisol results after standard dose SST.

Studies	Failed at 30 min but passed at 60 min	Passed at 30 min but failed at 60 min
Mansoor et al (13)	27/236 (12%)	1/236 (0.4%)
Chitale et al (14)		
• Institution 1	18/250 (7%)	0/250 (0%)
• Institution 2	15/134 (11%)	0/134 (0%)
• All	33/384 (9%)	0/384 (0%)
Struja et al (15)	39/400 (9.75%)	5/400 (1.25%)
Zueger et al (16)	10/73 (13.7%)	0/73 (0%)
Current Study	72/759 (9.5%)	0/759 (0%)

CL = confidence level, Std Err Dif = standard error of difference.

medical notes. As this test is associated with a risk of allergic reaction and is expensive to run, the justification of performing it is crucial from a clinical, medicolegal, economical and insurance coverage perspective. The UK wide national audit of SST outcomes showed that 47% of the respondents did not record indications for the test.[18] This reflects poor medical documentation and the need for effective medical documentation. We plan to disseminate these results to our medical colleagues through the institutional quality management team.

Our study included patients who underwent standard dose of SST alone. We therefore cannot advocate if one test is superior to the other. Our institutional practice allows the clinicians to use their discretion in the choice of the standard dose for SST. However, different studies have shown conflicting results. An earlier meta-analysis by Dorin et al[19] and a more recent study by Ospina et al[20] have both shown that the standard and the low dose SST perform well and have similar diagnostic accuracy. Another meta-analysis by Kazlauskaite et al[12] showed that the diagnostic value of LDSST was superior to the standard dose SST. These studies contrast with that of Kazlauskaite et al who had different inclusion criteria; they excluded 12 studies that were included in Dorin's earlier meta-analysis and included 3 new studies. A more recent study, involving 804 patients who had either a low dose or standard dose SST, reported that both tests were comparable for differentiating Addison's disease.[15]

Our study has the following strengths including: a large sample size with generalizability in terms of age, sex, body habitus, and reflected daily clinical practice; it is the largest study on this subject to the best of our knowledge; and no previous studies have reported on this subject from our geographical area. Therefore, this research adds valuable information to the literature. Since different cortisol assays have different sensitivity and specificity, we used the same assay to perform all tests to ensure accuracy of the results.

Our study has some limitations. First, we used retrospective data from a single-center, and therefore, a prospective study would help in further confirm these findings. Secondly, these results are applicable only to patients with standard-dose SST; therefore, it will be of interest to compare these outcomes to those of other studies assessing low dose SST and ITT. Furthermore, we were unable to determine why in most cases clinicians performed the test, since the indications for the test were not recorded in the medical records. In addition, we could not determine whether hypoadrenalism was due to primary or secondary causes due to a lack of ACTH results in most cases. Our database had SST performed at different times during the day and therefore baseline serum cortisol and ACTH levels are not necessarily the early morning levels. Finally, although we thoroughly checked the medical and prescription records and excluded women on oral contraceptives, some women might have received these medications from other institutions. Thus, there is a possibility that some women who are on contraceptives might have been included.

6. Conclusion

A 30-minute serum cortisol level following ACTH injection might lead to a false positive diagnosis of adrenal insufficiency as some patients cross the threshold cortisol levels only at 60 minutes. This practice can lead to a lifelong exposure to unnecessary treatment with exogenous steroids that can have harmful effects, including increased healthcare costs related to over-prescribing, monitoring, physician time, and enormous emotional and psychological impacts on patients. With patients in the 30-minute SST only protocol for cortisol measurement with an inadequate response, a repeat test should be done for up to 60 minutes if a robust basal to 30-minute cortisol change was observed.

To simplify the protocol, we advocate a 60-minute cortisol assessment after ACTH injection, which can identify all normal and abnormal results. Elimination of the 30-minute serum cortisol measurement will also help reduce the time spent by nurses in conducting this test. Patients will also enjoy a reduction in the frequency of venesection as fewer cortisol samples will be required. A morning basal cortisol level of over 226 nmol/L should be considered as the reliable threshold for adequate adrenal function when clinicians have low pretest adrenal insufficiency probability.

Acknowledgments

The authors would like to thank the Clinical Pharmacist, Mohamed Ahmed for the support.

Author contributions

Conceptualization: Muhammad Imran Butt.
Data collection and curation: Hadeel Aljamei, Lama Amer, Muhammad Sohaib Khan, Eman Alrajhi, Anhar Alnassar, Reem Alahmed, Mohammed Abufarhaneh, Fayha Farraj Abothenain, Dina Mahmoud Ahmad Aljayar.
Methodology: Muhammad Imran Butt, Muhammad Riazuddin, Lama Amer.
Project administration: Muhammad Imran Butt.
Review and editing: Muhammad Imran Butt, Nouf Alzuhayri.
Statistical design: Edward De Vol, Nouf Alzuhayri, Reem Alahmed.
Writing Manuscript: Muhammad Imran Butt.

References

[1] Plumpton FS, Besser GM. The adrenocortical response to surgery and insulin-induced hypoglycaemia in corticosteroid-treated and normal subjects. Br J Surg 1969;56:216–9.
[2] Carr PJ, Millar RP, Crowley H. A simple radioimmunoassay for plasma cortisol: comparison with the fluorimetric method of determination. Ann Clin Biochem 1977;14:207–11.
[3] Moore A, Aitken R, Burke C, et al. Cortisol assays: guidelines for the provision of a clinical biochemistry service. Ann Clin Biochem 1985;22:435–54.
[4] Cho HY, Kim JH, Kim SW, et al. Different cut-off values of the insulin tolerance test, the high-dose short Synacthen test (250 μg) and the low-dose short Synacthen test (1 μg) in assessing central adrenal insufficiency. Clin Endocrinol. 81:77-84.
[5] Lindholm J, Kehlet H. Re-evaluation of the clinical value of the 30 min ACTH test in assessing the hypothalamic-pituitary-adrenocortical function. Clin Endocrinol 1987;26:53–9.
[6] Dorin RI, Qiao Z, Qualls CR, et al. Estimation of maximal cortisol secretion rate in healthy humans. J Clin Endocrinol Metab 2012;97:1285–93.
[7] Alía P, Villabona C, Giménez O, et al. Profile, mean residence time of ACTH and cortisol responses after low and standard ACTH tests in healthy volunteers. Clin Endocrinol (Oxf) 2006;65:346–51.
[8] Longui CA, Vottero A, Harris AG, et al. Plasma cortisol responses after intramuscular corticotropin 1-24 in healthy men. Metabolism 1998;47:1419–22.
[9] Davies MJ, Howlett TA. A survey of the current methods used in the UK to assess pituitary function. J R Soc Med 1996;89:159–64.
[10] Yip CE, Stewart SA, Imran F, et al. The role of morning basal serum cortisol in assessment of hypothalamic pituitary-adrenal axis. Clin Invest Med 2013;36:E216–22.
[11] Watts NB, Tindall GT. Rapid assessment of corticotropin reserve after pituitary surgery. JAMA 1988;259:708–12.
[12] Kazlauskaite R, Evans AT, Villabona CV, et al. Corticotropin tests for hypothalamic-pituitary- adrenal insufficiency: a metaanalysis. J Clin Endocrinol Metab 2008;93:4245–53.
[13] Mansoor S, Islam N, Siddiqui I, et al. Sixty-minute post-Synacthen serum cortisol level: a reliable and cost-effective screening test for excluding adrenal insufficiency compared to the conventional short Synacthen test. Singapore Med J 2007;48:519–23.
[14] Chitale A, Musonda P, McGregor AM, et al. Determining the utility of the 60 min cortisol measurement in the short synacthen test. Clin Endocrinol (Oxf) 2013;79:14–9.
[15] Struja T, Briner L, Meier A, et al. Diagnostic accuracy of basal cortisol level to predict adrenal insufficiency in cosyntropin testing: results from an observational cohort study with 804 patients. Endocr Pract 2017;23:949–61.
[16] Zueger T, Jordi M, Laimer M, et al. Utility of 30 and 60 minute cortisol samples after high-dose synthetic ACTH-1-24 injection in the diagnosis of adrenal insufficiency. Swiss Med Wkly 2014;144:w13987.
[17] Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016;101:364–89.
[18] Chatha KK, Middle JG, Kilpatrick ES. National UK audit of the short synacthen test. Ann Clin Biochem 2010;47(Pt 2):158–64.
[19] Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med 2003;139:194–204.
[20] Ospina NS, Al Nofal A, Bancos I, et al. ACTH stimulation tests for the diagnosis of adrenal insufficiency: systematic review and meta-analysis. J Clin Endocrinol Metab 2016;101:427–34.