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Evaluation of the role of hydrocortisone either alone or combined with fludrocortisone in the outcome of septic shock in adults

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Abstract

Background: Management of sepsis is a time critical procedure; the consequences of improperly managed sepsis and septic shock can cause multiple organ dysfunction and death. The aim of this study was to evaluate of the role of hydrocortisone either alone or with fludrocortisone on the outcome septic shock in adults. This study was conducted on 66 patients who were assigned randomly to 3 groups each containing 22 patients. Control group had received standard therapy for sepsis, and H group had received standard therapy for sepsis plus hydrocortisone. HF group had received standard therapy for sepsis plus hydrocortisone and fludrocortisone.

Results: It showed that the use of corticosteroids (the hydrocortisone or the hydrocortisone plus fludrocortisone) in septic patients was associated with significant reduction in the time to wean from vasopressors and length of intensive care unit stay. Meanwhile, there were no significant effect of the mortality rate, Sepsis-Related Organ Failure Assessment (SOFA) score reduction, gastrointestinal bleeding, and superinfection as corticosteroids adverse effects between the three groups.

Conclusions: The corticosteroids in septic shock have significant positive impacts on some aspects in treatment of septic shock but it does not affect the mortality rate of the patients.

Keywords: Fludrocortisone, Hydrocortisone, Sepsis, Septic shock

Background

Infection can cause multiple symptoms when combined they cause systemic inflammatory response syndrome (SIRS), i.e., sepsis (Delano & Ward, 2016). Sepsis is a condition that is manifested clinically by physiological, biological, and biochemical abnormalities, and its main cause is the uncontrolled inflammatory response of infection. There are many definitions to sepsis but the latest and currently used was placed in 2016 and is known as SEPSIS 3, and it states that sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (Gül et al., 2017; Horak et al., 2019; Napolitano, 2018). While septic shock is defined as "a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone which can reach up to 40%" (Napolitano, 2018; Font et al., 2020). The consequences of improperly managed sepsis can cause multiple organ dysfunction and death (Gupta et al., 2016). Management of sepsis is a time critical procedure that should be started once the diagnosis is reached by trained equipped personnel (Evans, 2018; Hotchkiss et al., 2016). This helps in limitation of organ dysfunction and decreasing the complications and enhancing the survival rate. Factors affecting the prognosis of the septic shock are bacterial pathogenicity, time elapsed, and host condition (immunity status and comorbidities). These factors make the treatment customized to every case as

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these cases need multiple, diverse, and rapid management strategies (Vincent, 2018). Adjunctive methods to fight the dysregulation response caused by the body as a response to sepsis by: systemic steroids, ascorbic acid (vitamin C) and thiamine (Delano & Ward, 2016; Marik, 2018).

In conditions characterized by inflammation, the adrenal gland fail to properly produce cortisol, at these cases the supplementary treatment by corticosteroids is required (Williams, 2018)**.** The use of the hydrocortisone is recommended where patients are poorly responsive to fluids and vasopressors (Annane et al., 2020). According to the fourth revision of the surviving sepsis campaign, the use of the hydrocortisone is recommended to the cases where patients are poorly responsive to fluids and vasopressors. After the last revision of the sepsis campaign, two trials have been carried out to understand the benefits and risks of corticosteroids for adults with septic shock (Annane et al., 2020). The ADRENAL trial which evaluated the effect of hydrocortisone on septic shock patients and the APROCCHSS trial which evaluated the effect of hydrocortisone and fludrocortisone together, the results of those two trials favor the effect on the hydrocortisone and fludrocortisone on the mortality rate of the septic shock patients (Delano & Ward, 2016; Venkatesh et al., 2019).

Intravenous hydrocortisone (200 mg/day) is considered the medication of choice in shock reversal in patients suffering from septic shock and did not achieve hemodynamics with fluid resuscitation in addition to the vasopressors. The treatment with steroids has many several side effects like hyperglycemia and hypernatremia even though it might be lifesaving (Lee & Bainum, 2017; Venkatesh et al., 2018). Adding fludrocortisone to the commonly used hydrocortisone regimen may account for the positive results, but further studies are needed to confirm this (Lee & Bainum, 2017; Annane et al., 2018). This study was carried out to evaluate of the role of hydrocortisone either alone or with fludrocortisone on the outcome septic shock in adults.

Methods

This study was conducted at the intensive care unit (ICU) of Ain Shams University Hospitals. It was a prospective single blinded (only the patient was blinded) randomized controlled clinical study. After approval of the ethical committee of the institution, trial registration (ClinicalTrial.gov, NCT04492280), and obtaining a written informed consent from all patients or their legal guardians, the study was conducted between September 2018 and September 2020 on 66 patients subdivided randomly via computer closed envelopes method into 3 equal groups, 22 patients for each group: group C (control group), group H (hydrocortisone), and group HF (hydrocortisone and fludrocortisone).

Group C

These patients received standard therapy for sepsis which include the following: Measure lactate level, obtain blood cultures prior to administration of antibiotics, administer broad spectrum antibiotics, administer 30 mL/kg crystalloid for hypotension or lactate 4 mmol/L, apply vasopressors: norepinephrine as the first-choice vasopressor (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mmHg, source control: specific anatomic diagnosis of infection requiring emergent source control, mechanical ventilation if indicated, e.g., Glasgow coma score < 8, stress ulcer prophylaxis: either proton pump inhibitors or histamine-2 receptor antagonists, nutritional support with early parenteral nutrition whenever possible, venous thromboembolism prophylaxis pharmacologic prophylaxis (unfractionated heparin or low-molecular-weight heparin), and blood sugar control: upper blood glucose level ≤ 180 mg/dL, glucose values will be monitored every 1 to 2 h until glucose values and insulin infusion rates are stable, then every 4 h thereafter in patients receiving insulin infusions.

Group H

These patients received standard therapy for sepsis plus hydrocortisone (Solucortef®, E.I.P.I.co. under license of Pfizer) at dose 50 mg every 6 h by intravenous route.

Group HF

These patients received standard therapy for sepsis plus hydrocortisone (Solucortef®) at dose of 50 mg every 6 h by intravenous route and fludrocortisone (Cortilon®, Amoun) 50 µg once daily by nasogastric tube for 1 week.

Patients included in this study were between 18 and 80 years old, both sexes who were suffering from septic shock and had any of the following criteria: clinical evidence of infection within the previous 72 h of ICU admission or Sepsis-Related Organ Failure Assessment (SOFA) score of 3 or 4 (on a scale of 0 to 4 for each of six organ systems) for at least 2 organs and at least 6 h or vasopressors therapy (norepinephrine, epinephrine, or any other vasopressors at a dose of ≥ 0.25 µg/kg/min) for at least 6 h to maintain a systolic blood pressure of at least 90 mmHg or mean blood pressure of at least 65 mmHg. The reasons for exclusion included **r**efusal of patient or legal guardian to consent to participate in the study, pregnancy, lactation, and gastrointestinal bleeding.

The study end points were either improvement of the patient in the form of maintaining MAP ≥ 65 mmHg without vasopressors or death of patient. The primary

outcome is the mortality rate due to septic shock. The secondary outcomes were the following: first, the time of weaning from vasopressors (in days). The number of days each patient required to cease the usage of vasopressors in their treatment regimen. Then, the mean number of days in each group was calculated to detect the statistical significance. Second, the SOFA score was calculated and recorded for each patient in every group on admission (baseline) and on a daily basis. Then, the mean value for each group everyday was calculated to check for statistically significant difference between the three groups. Third the duration of ICU stays due to septic shock as a cause (in days). The number of days each patient would spend in the ICU until they leave (either due to discharge or death). Then the mean number of days spent in each group was calculated to detect for the statistical significance between the three different groups. Fourth the complications of steroids: any complication that appeared on any of the patients was recorded and the total of each complication was calculated to give the percentage of the presence of this complication in each group to measure the effect of steroid therapy.

Statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS Statistics) for Windows, version 20 (IBM© Corp., Armonk, NY, USA). For quantitative data, the Shapiro-Wilk test for normality was performed. Normally distributed data were summarized as mean and standard deviation (SD). The studied groups were compared using ANOVA and post-hoc paired *t* test when the results were significant. Qualitative data were summarized as frequencies and percentages, and associations were tested using the chi-square test. A p value < 0.05 was considered significant.

Sample size determination based on 0.05 power 0.8, Using G*power program, setting alpha error at 5% and power at 80% assuming an effect size of 0.4 per the combination of hydrocortisone and fludrocortisone on the outcome of septic shock patients, the needed sample will be 66 patients subdivided into 3 equal groups, 22 patients for each group. Random allocation sequence was generated using Random.org to assist in locating the patients in one of the three groups with reducing the chance of bias. The technique employed in this study was the simple random technique where the sequence was generated an opaque envelope containing folded papers having the number of the patients. The only side who blinding was applied to was the patient.

Results

The number of patients who were equally randomized in the three groups was 66 patients (22 patients in each group). They all received the intended treatment and were analyzed for the primary outcome and secondary outcomes. The study started on September 2018 and ended by September 2020; during this period, the patients were selected and randomly located to the different groups. The study ended by both the improvement and dismissal of the patient from the ICU or the death of the patient. There was no long-term follow-up in the design of this study.

The three groups were comparable to gender and age showed no statistically significant difference between the three groups when compared separately to each other (P1, P2, and P3) and when compared collectively. Meanwhile, the SOFA baseline score showed no statistically significant difference (Table 1).

The mortality rate showed lack of statistical significance between the three groups ($P=0.822$). Also, the comparison between the control group (40.9%) and H group (31.8%) showed no statistically significant difference (P1 = 0.531), the comparison between the control group (40.9%) and the HF group (36.4%) showed no statistically significant difference (P2 = 0.757) and the comparison between the H group (31.8%) and HF group (36.4) showed no statistically significant difference (P3 = 0.750) (Fig. 1).

Table 1 Comparison between the three groups regarding the demographic data and baseline SOFA score

	Control group ($N=22$)	H group ($N=22$)	HF group ($N=22$)	Tests				
				f/χ^2	*P* value	P1	P2	P3
Age (years)								
Mean ± SD	61.86 ± 4.42	60.59 ± 5.75	61.77 ± 4.88	1.203	0.307	0.663	0.775	0.276
Sex								
Female	8(36.4%)	7(31.8%)	8(36.4%)	0.133	0.935	0.750	1.000	0.750
Male	14(63.6%)	15(68.2%)	14(63.6%)					
SOFA Baseline								
Mean ± SD	9.14 ± 1.98	8.36 ± 1.76	8.59 ± 1.79	1.017	0.368	0.354	0.593	0.912

SD standard deviation, *N* number, *H group* group receiving hydrocortisone, *HF group* group receiving hydrocortisone plus fludrocortisone, *P1* comparison between the control group and H group, *P2* comparison between the control group and HF group, *P3* comparison between the H group and HF group

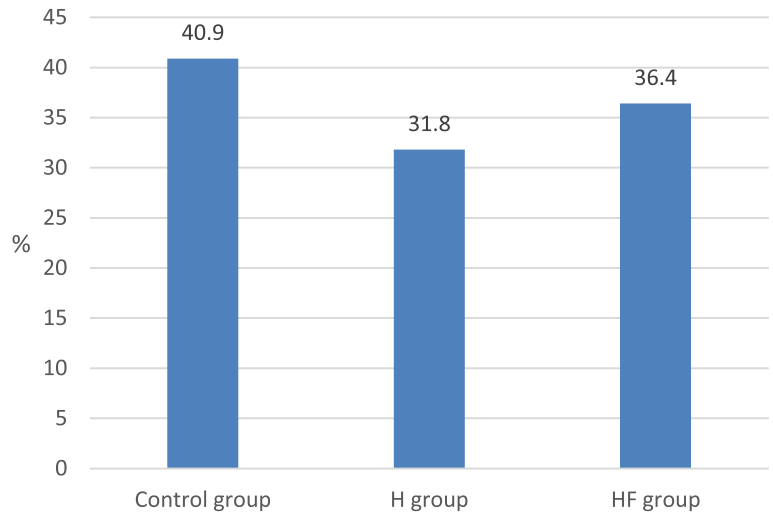

Fig. 1 Comparison between the three groups regarding the mortality rate

The Three groups showed statistically significant difference when it came to comparing the time to wean from vasopressors. The control group (10.38 ± 1.19) with H group (9.27 ± 1.39) and HF group (9 ± 0.96) regarding the time of weaning of vasopressor ($P = 0.011$). While was non-statistically significant deference between H group (9.27 ± 1.39) and HF group (9 ± 0.96) (P3 = 0.822). The comparison between the control group (10.38 ± 1.19) and H group (9.27 ± 1.39) showed statistically significant difference (P1 = 0.047), the comparison between the control group (10.38 ± 1.19) and the HF group (9 ± 0.96) showed statistically significant difference (P2 = 0.013), and the comparison between the H group (9.27 ± 1.39) and HF group (9 ± 0.96) showed no statistically significant difference (P3 = 0.822) (Table 2).

Meanwhile, the length of ICU stay showed statistically significant difference when comparing the three groups; control group (11.36 ± 1.33) with H group (10.27 ± 1.7) and HF group (10.14 ± 1.39) regarding the duration of ICU stay ($P = 0.014$). The comparison between the control group (11.36 ± 1.33) and H group (10.27 ± 1.7) showed statistically significant difference (P1 = 0.045), the comparison between the control group (11.36 ± 1.33) and the HF group (10.14 ± 1.39) showed statistically significant difference (P2 = 0.021) and the comparison between the H (10.14 ± 1.39) group and HF group (10.27 ± 1.7) showed no statistically significant difference (P3 = 0.950) (Table 3).

The complications of steroid therapy did not show any statistically significant difference except when comparing the effect of steroid therapy on hyperglycemia (Fig. 2).

In the gastrointestinal tract (GIT) bleeding as a complication to steroid therapy, the comparison between the control group (22.7%) and H group (40.9%) showed no statistically significant difference (P1 = 0.195), the comparison between the control group (22.7%) and the HF group (50%) showed no statistically significant difference (P2 = 0.060) and the comparison between the H group (40.9%) and HF group (50%) showed no statistically significant difference (P3 = 0.545). Moreover, it showed no statistically significant difference between the three groups ($P = 0.165$).

In the superinfection as a complication to steroid therapy, the comparison between the control group (13.6%) and H group (27.3%) showed no statistically significant difference (P1 = 0.262), the comparison between the

Table 2 Comparison between the three groups regarding the time to wean from vasopressors

				ANOVA		P1	P2	P3
	Control group (*N* = 22)	H group (*N* = 22)	HF group (*N* = 22)	*f*	*P* value			
Time of weaning of vasopressor (days)	10.38 ± 1.19	9.27 ± 1.39	9 ± 0.96	5.036	0.011*	0.047*	0.013*	0.822

N number, *H group* group receiving hydrocortisone, *HF group* group receiving hydrocortisone plus fludrocortisone, *P1* comparison between the control group and H group, *P2* comparison between the control group and HF group, *P3* comparison between the H group and HF group

*Significant

Table 3 Comparison between the three groups regarding the duration of ICU stay

				ANOVA		P1	P2	P3
	Control group (*N* = 22)	H group (*N* = 22)	HF group (*N* = 22)	*f*	*P* value			
Duration of ICU stay (days)	11.36 ± 1.33	10.27 ± 1.7	10.14 ± 1.39	4.543	0.014*	0.045*	0.021*	0.950

N number, *H group* group receiving hydrocortisone, *HF group* group receiving hydrocortisone plus fludrocortisone, *P1* comparison between the control group and H group, *P2* comparison between the control group and HF group, *P3* comparison between the H group and HF group *Significant

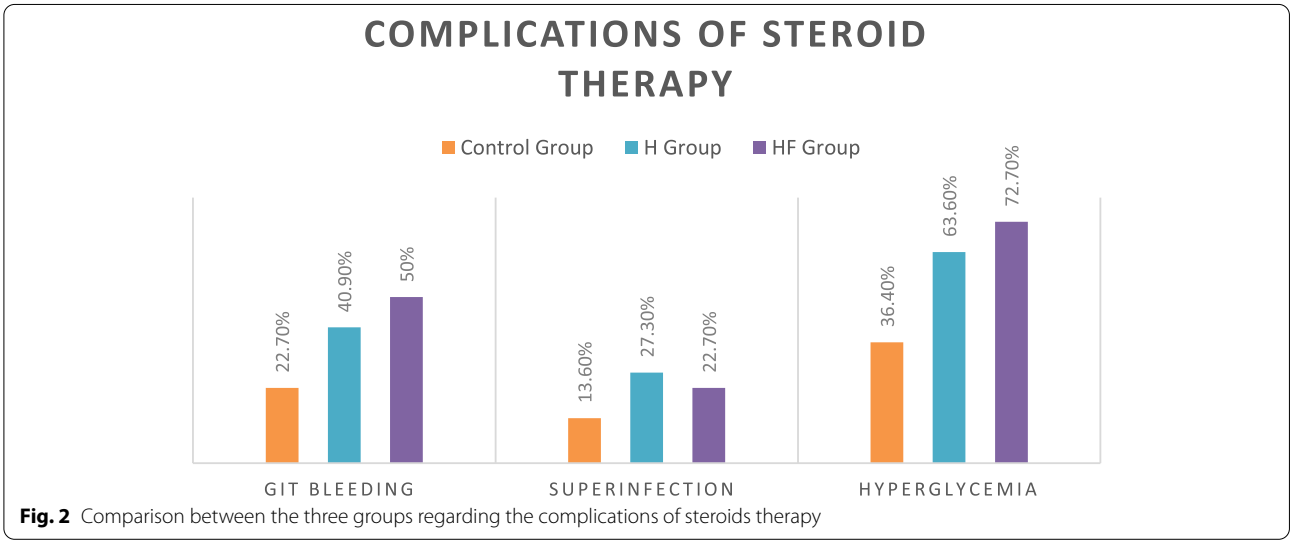

Fig. 2 Comparison between the three groups regarding the complications of steroids therapy

control group (13.6%) and the HF group (22.7%) showed no statistically significant difference (P2 = 0.434) and the comparison between the H group (27.3%) and HF group (22.7%) showed no statistically significant difference (P3 = 0.728). Moreover, it showed no statistically significant difference between the three groups (*P* = 0.530).

In the hyperglycemia as a complication to steroid therapy, the comparison between the control group (36.4%) and H group (63.6%) showed no statistically significant difference (P1 = 0.070), the comparison between the control group (36.4%) and the HF group (72.7%) showed statistically significant difference (P2 = 0.015), and the comparison between the H group (63.6%) and HF group (72.7%) showed no statistically significant difference (P3 = 0.517). Moreover, it showed statistically significant difference between the three groups (*P* = 0.040).

Discussion

In this study, it was found that the mortality rate was statistically non-significant between the three groups when compared to each other. The lack of the statistical significance between the three groups might be due to the sample size, the wide age range under which this study was carried on. In addition to that, this study focuses on the short-term mortality rate and it lacks a long-term follow-up. In a study conducted by Venkatesh et al. on whether the hydrocortisone in comparison to a placebo group receiving the standard therapy would reduce the mortality among the septic shock patients, the mortality rate was found to be statistically non-significant (Venkatesh et al., 2018). Meanwhile, Annane et al. contradicted those results in a study that was conducted to evaluate the clinical outcomes on septic shock patients after receiving steroid therapy using hydrocortisone plus fludrocortisone. Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group than in the placebo group at ICU discharge (*P* = 0.04). The difference in the results was explained by the authors that adding mineralocorticoid treatments showed a significant NF-κB–mediated down-regulation of vascular mineralocorticoid receptors (Annane et al., 2018).

In this study, the time to wean from the vasopressors in the ICU improved in the hydrocortisone group and the hydrocortisone plus the fludrocortisone group showed a statistically significant difference. Those results can explain that both the hydrocortisone alone or the hydrocortisone plus fludrocortisone have a positive impact on the status of the septic shock which consequently reduce the time needed to wean from vasopressors and that is one of the outcomes that this study was carried out for.

In a review conducted by Yamamoto et al. (2020), the patients in the dual corticosteroid treatment group had a higher rate of shock reversal and more vasopressor-free days than patients in the control group and this coincides with our study (Yamamoto et al., 2020). On the other hand, Annane et al. (2010) compared two groups one received hydrocortisone and the other received hydrocortisone plus fludrocortisone, and it showed that the difference in the number of vasopressor free days had no statistically significant difference ($P=0.62$) and that contradicted with the results of our study. This may be due to the difference in the sample size which was larger in this study ($N=509$). The candidates to this study were receiving insulin with different doses that might have been one of the causes to this difference (Annane et al., 2010).

The duration of the ICU stay was shorter in the hydrocortisone group and the hydrocortisone plus fludrocortisone group than the control group. There was statistically significant difference between the control group and the hydrocortisone group and hydrocortisone plus fludrocortisone. Venkatesh et al., in their study, showed that the length of stay of the patients receiving hydrocortisone as a treatment was shorted than that of the patients receiving the standard protocol of treatment, and this difference showed a statistically significant difference ($P<0.001$) and that agrees with the results of our study. This was explained in that study by the authors by the method of hydrocortisone administration which was continuous infusion which enhances the inflammatory response and shock reversal. Moreover, non-tapering discontinuation mechanism was used as it shows a beneficial effect on the survival rate (Venkatesh et al., 2018). On the contrary, Sprung et al. (2008) performed a study where the patients received hydrocortisone and other patients to receive placebo. The length of ICU stay result contradicted our study where there is no statistically significant difference between the groups ($P=0.51$). It was explained by the authors that this result may be caused by the lack of relation to the adrenal insufficiency, and that the time of ICU stay may be related to vascular hypo-reactivity. It may be due to a more widespread anti-inflammatory action of corticosteroids, which inhibit the expression of pro-inflammatory cytokines, mediators, and receptors (Sprung et al., 2008).

The steroid therapy complications recorded in this study were the following: GIT bleeding, superinfection and hyperglycemia. The GIT bleeding has a lack of statistically significant difference between the three groups, the superinfection also showed lack of statistically significant difference between the three groups, and the hyperglycemia showed statistically significant difference only in the group comparing the HF group and the control group. Yamamoto et al. in their study showed that hydrocortisone plus fludrocortisone treatment revealed that risks of superinfection and GIT bleeding were similar between the intervention and the control groups (Yamamoto et al., 2020). Meanwhile, the incidence of hyperglycemia was higher in patients treated with both hydrocortisone and fludrocortisone than the control group and this agreed with the results of our study. It was explained by the authors that the hyperglycemia is a normal adverse event related to the administration of hydrocortisone, while the superinfections and GIT bleeding were related more to the addition of fludrocortisone to hydrocortisone treatment. Annane et al. reported many adverse effects in their study, the superinfection showed statistically significant difference between the hydrocortisone group and the hydrocortisone plus fludrocortisone group ($P=0.02$). Those results contradict the results of our study. Those results might be explained by the fact that the candidates in this study received different doses of insulin as regimen of the treatment (Annane et al., 2010).

The limitations in this study can be that these non-significant effects may be related to the dosage of the corticosteroids in this study, small sample size or due to the condition of the patients admitted in the study (SOFA score). The recommendation for the future studies to experiment different drug doses with different speed of administration, increase the sample size and specify the state of the patient at the beginning of the studies (SOFA score). Also, we recommend to take into considerations the complications caused by the corticosteroids. In addition to that, we recommend designing a study to be more age specific (ex. To exclude the geriatric patients).

Conclusions

We concluded from this study that the use of corticosteroids in the ICU may have a significant role in reducing the time to wean from vasopressors in the septic patients, reduction in the length of ICU stay and reduction of the SOFA score. Meanwhile, there was no significant effect of the corticosteroids on the death rate of the septic patients in the ICU and on the GIT bleeding and superinfection complications of the corticosteroids.

Abbreviations

ANOVA: Analysis of variance; GIT: Gastrointestinal tract; ICU: Intensive care unit; MAP: Mean arterial pressure; SIRS: Systemic inflammatory response syndrome; SOFA: Sepsis-Related Organ Failure Assessment.

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Authors' contributions

HL, AH, AK, SW, and MA have full access to all the data in the study and take responsibility for the integrity of the data. Study concept and design: HL, AH, and AK; acquisition of data: AH, AK, SW, and MA; analysis of data and

critical revision of the manuscript: SW, AK, and MA. All authors have read and approved the final manuscript.

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Availability of data and materials
We intend to share the study protocol as well as the individual de-identified participants' data. Data will be accessible through direct contact with the corresponding author, beginning 12 months and ending 24 months following article publication.

Declarations

Ethics approval and consent to participate
The study obtained approval from the ethical committee of the Faculty of Medicine, Ain Shams University, Egypt (MD 176/2018). The study was registered at ClinicalTrials.gov (NCT04492280; July 30, 2020; https://clinicaltrials.gov/ct2/show/NCT04492280). Informed written consents were obtained from all patients or their legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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