Influence of Pharmacokinetics in Responders and Non-Responders of Prednisolone Based Therapy in Alcoholic Hepatitis Patients

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Abstract

Background: Corticosteroids used to reduce short-term mortality in patients affected with severe alcoholic hepatitis. However, there are no independent studies associated with responders and non-responders in terms of the Lille score and pharmacokinetics.

Objectives: The study’s objective is to compare the Lille score and pharmacokinetics of alcoholic hepatitis patients after the intake of prednisolone drug.

Methods: The total number of 24 patients were included out of that 8 patients were excluded due to intestinal bleeding, peptic ulcer and sepsis. Remaining 16 patients were analyzed for biochemical parameters to check alcoholic hepatitis condition.

Results: The increase in liver enzyme marker such as AST, ALT, and ALP and Maddrey discriminant function (MDF) score more than 32 was observed in patients which indicates the severity of alcoholic hepatitis. Later 4 patients were withdrawn from the studies, so that total of 12 patients were investigated for Lille score and pharmacokinetics. We used 7 days of periodic intake of prednisolone drug to identify the treatment effectiveness in alcoholic patients. After the end of 7 days of prednisolone treatment, changes in Lille score was observed among the patients. Based on this Lille score, responders and non-responders are categorized. Further, the pharmacokinetics study for prednisolone responders and non-responders was investigated to determine the differences in Tmax, Cmax, area under the curve (0–24 and (0–∞), and half-life values. The difference in Tmax, Cmax, area under the curve, and half-life values between responders and non-responders was not significant.

Conclusion: Our result suggests that prednisolone has an effect on Lille score, despite no changes in pharmacokinetics. Early switching to another drug has no benefit for non-responders to corticosteroids. As a result, the problem of non-responder management remains unsolved in pharmacokinetics studies, and it requires further research in more patients at the molecular level.

Keywords: Alcoholic hepatitis, Prednisolone, Pharmacokinetics, MDF score, Lille score.

1. INTRODUCTION

Binge drinking leads to alcohol hepatitis (1). Approximately 20% of heavy drinkers will develop AH (1,2). Acute liver failure (ALF) is prevalent in cirrhosis patients, although the symptoms start with systemic inflammation and jaundice. (3,4). Recovery is achieved through natural and reparative methods, such as alcohol withdrawal and supportive and symptomatic care. There is a high mortality rate and slow improvement after prolonged hospitalization for those with severe cases (5,6). From a histologic picture of acute hepatic cell injury, many patients progress to cirrhosis over time. Recently, there has been interest in using corticosteroid therapy in this disease in the hopes of lowering mortality, shortening convalescence time, and preventing the progression to cirrhosis (7).

Corticosteroids are widely used for treating people with liver disease for over 20 years, and some of the controlled clinical studies have found that prednisolone has a significant therapeutic effect in active chronic hepatitis (8). Prednisone, a synthetic corticosteroid with anti-inflammatory and immunosuppressive properties, has been used as treatment strategy for over several decades (9). Prednisolone was reported to alter the molecular expression of proinflammatory cytokine genes, as well as to
prevent humoral and cell-mediated autoimmunity by inhibiting the signal transduction of several immune cells (10,11). Previous study report that, prednisone therapy significantly reduced the mortality of alcoholic hepatitis and hepatic encephalopathy, while the other found no statistically significant difference in patient mortality rates (12,13). Prednisolone metabolism and plasma protein binding in patients with liver disease are, however, poorly understood. Drug regimens and dosages vary widely and are often chosen at random, based on the assumption that the steroids' biological half-life is normal. Although unproven, it is widely assumed that prednisone is consistently converted to the biologically active prednisolone even by diseased livers, and that these compounds are thus therapeutically equivalent (14) [Fig. 1]. Even though the prednisolone was widely used in AH treatment due to their side effects like peptic ulcer, esophageal varices and intestinal bleeding. The in-depth knowledge about their pharmacokinetics studies and clinical application are lacking (15). We hypothesized that inter-individual differences in prednisolone PK might explain some of the differences in prednisone treatment response and non-responders in AH patients.

Objectives

The main objective of the study was to compare the prednisolone PK in AH patients after dosing with the Lille score of responders and non-responders.

2. Methods

2.1. Patients

SRM Medical College Hospital and Research Centre’s SRMIST Board of Ethics has approved this research (Grant No. 2363/IEC/2021). The study is based on a prospective analysis of patients who were diagnosed early with alcoholic hepatitis at admission and were admitted with AH between May 2021 and February 2022 in the SRM Medical College Hospital and Research Centre, Chennai, after acquiring consent and assent. All of the patients who were included had previously been diagnosed with alcoholic hepatitis using accepted criteria, such as standard ultrasound with hepatomegaly and heterogeneous liver parenchyma, splenomegaly, and signs of portal hypertension, which was then confirmed with endoscopy in the presence of esophageal or gastric varices or portal hypertensive gastropathy [Fig. 2]. The presence of neoplasia, hepatorenal syndrome, active hepatitis B or C, suspected autoimmune liver disease, or drug-induced liver disease were defined as exclusion criteria in this study, as were uncontrolled acute infections and active stomach ulcers as contraindications to corticosteroids. The following conditions had to be met in order for a patient to be diagnosed with AH and be included in the study group: recent onset of jaundice in a patient with a history of heavy alcohol use (40 g of alcohol per day for women and 60 g per day for men for >6 months), bilirubin >3 mg/dL, and an AST/ALT ratio of >1.5. There was no histological confirmation available. Alcoholic hepatitis patients [Maddrey discriminant function (MDF) score > 32] was found and subsequently studied from the initial AH group. Based on the MDF score the AH patients were classified in to two groups as responders and non-responders for prednisolone therapy. A gastroenterologist analyzed the patient's medical records to look for pertinent demographic data, lab results, and signs of alcohol-related hepatitis, such as disease activity. Anytime without jeopardizing their relationship with their healthcare provider, participants were free to walk away from the study.

2.2. Blood Collection

To examine for prednisolone treatment, a total of 24 AH patient was selected for this study with an age limit of (37.1±6.01). History of patient’s records was checked to see whether the patients has related disease condition of chronic hepatitis, acute variceal bleed, tuberculosis, uncontrolled diabetes, or deranged renal functions were all reasons for exclusion. Every eligible AH patients was considered and taken for biochemical analysis. Drug intake of patients was checked for the past three days prior to the sampling visit in order to get the most accurate medication history possible. After a fasting of at least 8 hours, oral prednisone (10).

Total volume of 4 ml blood was collected from patients with and without anticoagulant (2ml + 2 ml), from that serum was used for biochemical analysis and plasma was used for prednisolone pharmacokinetics analysis. The blood samples were collected in a tube containing no anticoagulant or preservative. Each tube was placed upright for 29 minutes at room temperature to allow it to clot completely, then centrifuged at 3,500 rpm for 10 minutes to isolate serum in a consistent manner to reduce pre-analytic variability (16).

2.3. Biochemical Serum Analysis

Prior to being chosen for the study, participants were subjected to a clinical screening procedure. To rule out possible
interference, serum samples were visually examined for hemolysis and lipemia. Serum biochemical marker for hepatitis such as bilirubin, ALT, AST, ALP, albumin, globulin, A/G ratio, creatinine, urea, prothrombine and GGT were measured by Roche diagnostic reagents (17-19). Following that, prognosis of AD were measured by MDF to check the severity of the AD disease in patients. MDF is the standard score used to predict the severity of AH and the need for treatment, and it is calculated as follows: 

\[ \text{score} = \frac{\text{exp}(R)}{1 + \text{exp}(R)} \]

where \( R = 3.19 - (0.10 \times \text{age}) + (0.147 \times \text{baseline albumin}) + (0.0165 \times \text{bilirubin level change}) - (0.206 \times \text{creatinine}) - (0.0065 \times \text{baseline bilirubin}) - (0.0096 \times \text{prothrombin time}) \) using total serum bilirubin values on Days 1 and 7 (3).

2.4. Pharmacokinetics

2.4.1. Sample Collection

The blood from the patients were withdrawn over a period of nine-hour, beginning at 7.00 a.m. and ending at 4.00 p.m at 7th day after dosing of prednisolone. For pharmacokinetics studies, the 1 hour before the intake of prednisolone drug in the morning the blood samples was collected and at 0.0, 0.5, 1.0, 2.0, 2.5, 3.0, 4.0, 6.0, 9.0, and 12.0 hours afterwards. A peripheral intravenous lines of 23 gauge catheter were used to obtain pharmacokinetics blood samples from the vein in hand. Proper institutional standard procedure was followed for withdrawing the blood using an indwelling catheter. For each patient blood collection, the duration of time and the number of attempts for taking blood through intravenous using catheter gauge were also noted. Following the guidelines the heparin was used to clean and flush the indwelling IV line between blood withdrawals. The entire blood collection in this study was not exceeded above 50 mL. The blood collection for the research purpose was calculated based on the body weight with a minimum of 30 kg, which represents the volume of blood lesser than 5%. 3 mL of blood was collected in potassium EDTA-containing tubes (Vacutainer® tubes) at each sampling time point. Once the blood was collected in the tube, they are inverted up and down to mix the blood, which is done for more than 3 times. Then these samples are stored in ice unstill further centrifugation process. The centrifugation process at 2,000 rpm for 10 minutes needed to complete before the 1 hour of blood sample collection. After the centrifugation, the plasma layer was separated and these samples was taken in a plastic tube and closed with polypropylene stopper. Each sample was properly labelled with date, time, and name of the patients. These sample were kept in 70°C for further analysis.

2.4.2. Sample Preparation

Protein precipitation was used to extract prednisolone from human plasma samples (11). In a polypropylene centrifuge tube, the plasma with a volume of 500 μL was added to the extract membrane integral protein with the mixture of deionized water (1.5 mL) and 0.5% of phosphoric acid. The detergent was removed using the 3 mL of ethyl acetate and the hydrophobic protein solubility was maintained. During centrifugation process, the tube cape was closed tightly and vortex was done for 2 minutes before being kept at the 2000 g for 15 minutes. The sample in the organic phase was then washed with 250 μL of sodium hydroxide and then transferred to 12 mL tubes for centrifugation at 2000 g. After the process under the nitrogen stream the organic phase was evaporated and dried and these deposits are dissolved in methanol (700 μL). The sample were injected into the chromatographic system in a volume of 20 μL and they were sonicated before usage.

2.4.3. Chromatographic Sample Analysis

Liquid chromatography-mass chromatography (LC-MS) 2020 system (Shimadzu, Japan) attached with LC10ADVP binary pump was used for the analysis. In mobile phase, acetonitrile, water (1), and formic acid (%) was used to separate the sample in the Phenomenex column (250 x 4.6 mm, 5 μm). The 20 μL of sample was injected and the 0.8 mL/min was set for the flow rate. After the 20 minutes of run time at the wavelength (λ) of 254 nm the sample was detected. For nebulization nitrogen gas was used in the flow rate of 1.5 L/min in the Mass (MS) compartment, which featured a single quadrupole mass spectrometer with an electrospray ionization (ESI) source. Curved desolvation line (CDL) and heat block temperatures were set at 250°C and 350°C, respectively. Utilizing Lab Solution Software, all the data were gathered and processed.

2.4.4. Prednisolone Quantification

The concentrations of drug in the blood were determined using LC-MS. To detect the spike in the plasma samples (50 μL), dexamethasone (1 μg/mL) was dissolved in acetonitrile. Further 150 μL of acetonitrile was added to the protein which are precipitated after the centrifugation at 15000 g for 15 minutes in 4°C. After that 100 μL of supernatant was added to the mobile phase which consist of 100 μL of Ammonium acetate (5 mM) and acetic acid (pH 4). From this mixture, the 50 μL was injected to the LC-MS. The final concentration of the prednisolone with 0-2000 ng/mL final concentration and dexamethasone were spiked with 50 μL of control plasma as previously mentioned to produce standard curve samples. Sigma provided the prednisolone and dexamethasone. Reverse phase chromatography was used to separate the analytes, with a Thermo Hypersil
Gold C18 column (50 5 mm; 5 m) and a Javelin Hypersil Gold (3 mm) pre-column. With a gradient flow of Mobile Phase A and acetonitrile, the mobile phase was delivered at a flow rate of 0.5 mL/min. The mobile phase was 20% acetonitrile for the first 30 seconds, then increased linearly to 90% acetonitrile over 4 minutes. After 1 minute at 90% acetonitrile, the concentration dropped linearly to 20% acetonitrile, which was held for another 30 seconds. Prednisolone and dexamethasone had retention times of 2.8 and 3.2 minutes, respectively. Tandem mass spectrometry was used to identify the analytes.

2.5. Pharmacokinetic Analysis

Using the Phoenix WinNonlin version 8.1., pharmacokinetic properties were measured from prednisolone plasma concentrations using a noncompartmental approach (11). Tmax was calculated as the corresponding time point for the occurrence of Cmax based on the observed concentrations. AUC0-t was calculated using the linear trapezoidal method until the last measurable plasma prednisolone concentration was reached, and AUC0-∞ was calculated using the formula AUC0-∞ = AUC0-t + Clast Ke. It was calculated using linear least square regression of the log concentration–time profile's last 3–4 time points. The terminal half-life was calculated using the formula t1/2 \(=\frac{0.693}{K_e}\).

2.6. Statistical Analysis

The sample size was estimated by the formula

\[ n = \frac{2SD^2(Z_{\alpha}/2+Z_{\beta})^2}{d^2} \]

where

- SD=6.50 standard deviation as per from previous studies
- \(Z_{\alpha}=1.96\) at 5% error(95% confidence interval)
- \(Z_{\beta}=0.84\) at 80% power
- d=5.2 effect size

The estimated sample size is 24.Total sample N=24

STATISTICAL ANALYSIS:

Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 Released 2013. Armonk, NY: IBM Corp., will be used to perform statistical analyses.

Descriptive Statistics:

Descriptive analysis of all the explanatory parameters will be done using mean and standard deviation for quantitative variables, frequency and proportions for categorical variables.

Inferential Statistics:

Student’s t-test will be used to compare the differences between the groups and paired t test will be used to compare different days.

The level of significance will be set at P<0.05.

And any other relevant test, if found appropriate during the time of data analysis will be dealt accordingly.

3. Results

3.1. Baseline Characteristic

In this study, 24 AH patients with both male and female genders with age category of 37.16±6.01 were investigated by following the guidelines. Out of 24 patients, 8 were considered as ineligible for prednisolone drug treatment due to sepsis, intestinal bleeding, and peptic ulcer. While 16 eligible patients are taken for biochemical analysis. The biochemical changes in the patients were analyzed in a preliminary study, and the results are shown in Table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(yrs)</td>
<td>Day 1 (Mean+SD)</td>
<td>Day 7 (Mean+SD)</td>
</tr>
<tr>
<td>Age(yrs)</td>
<td>37.1±6.01</td>
<td>37.1±6.01</td>
</tr>
</tbody>
</table>
3.2. Biochemical Analysis

The results showed that increase in level of liver enzyme such as ALT, AST, and ALP and biochemical parameters of liver function such as total bilirubin (15.37 ± 7.30 mg/dl), albumin (3.000± 0.66 gm/dl), globulin (3.667 ±0.43 gm/dl), A/G ratio (0.7517 ±0.20 gm/dl), creatinine (0.68 ± 0.22 gm/dl), urea (13.83± 6.43 gm/dl), prothrombine (18.73 ± 2.77 sec), and GGT (374.2 ± 210.6) were all increased in AH patients. The MDF score was greater than 32 for all the patients indicating severe alcoholic hepatitis. So that these patients are selected for the prednisolone treatment from Day 1 to Day 7.

3.3. Lille Score and PK Analysis

The LM score was calculated at the end of prednisolone treatment Day 7. The LM score less than 0.45 was observed in 6 patients they were indicated as responders and the LM score greater than 0.45 was observed in other 6 patients which indicates the non-responders. These indicates that out of 12 patients, 6 patients are responders and other 6 patients are non-responders to the prednisolone (Table 2).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDF Score</td>
<td>4.1</td>
<td>27.1</td>
</tr>
<tr>
<td>Lille Score</td>
<td>0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>AUC (0–24) (μg/ml*h)</td>
<td>44.94</td>
<td>38.73</td>
</tr>
<tr>
<td>AUC (0–∞) (μg/ml*h)</td>
<td>50.86</td>
<td>43.1</td>
</tr>
</tbody>
</table>

While similar Tmax value was observed in both responder (2.5± 0) and non-responders (2.5±0). Moreover, the same value of Cmax was observed in both responder (11.15±0.92) and non-responders (11.28±0.93). Interestingly, our results did not showed
a significant difference between the AUC (0–24) value in both responders (44.40±5.93) and non-responder (46.93±6.45). Also for the AUC (0–∞) the responders (48.94±6.41) and non-responders (51.37±6.52) to drug was observed with same range of value (Fig. 3; Table 3).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>2.5± 0</td>
<td>2.5±0</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>11.15±0.92</td>
<td>11.28±0.93</td>
</tr>
<tr>
<td>AUC(0–24) (µg/ml*h)</td>
<td>44.40±5.93</td>
<td>46.93±6.45</td>
</tr>
<tr>
<td>AUC(0–∞) (µg/ml*h)</td>
<td>48.94±6.41</td>
<td>51.37±6.52</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>3.36±0.79</td>
<td>3.36±0.94</td>
</tr>
<tr>
<td>CL/F [(mg)/(µg/ml)/h]</td>
<td>0.82±0.11</td>
<td>0.79±0.11</td>
</tr>
</tbody>
</table>

$T_{\text{max}}$ time required to achieve maximum plasma concentration; $C_{\text{max}}$ maximum plasma concentration; AUC (0–24) area under concentration–time curve extrapolated to 24 h; AUC(0–∞) area under concentration–time curve extrapolated to infinity; CL/F total body clearance; $t_{1/2}$ half-life.

4. Discussion

The most common cause of death from alcohol is alcohol-related liver disease (8,22,23). In the treatment of patients with AH, corticosteroid therapy is still the gold standard. In the absence of liver transplantation, steroid non-responders have few options, and mortality remains high (24). To improve outcomes in these patients, a high level of suspicion, systematic screening, and prompt, adequate treatment are required (22,25). For short-term survival, several researchers have prioritized treating severe forms of alcoholic hepatitis (1), as defined by a discriminant function of MDF > 32. Early identification of patients who do not benefit from corticosteroid treatment is critical when selecting candidates for new therapeutic strategies in order to progress in the management of patients treated with corticosteroids (26,27). To achieve this goal, we proposed a simple criterion for identifying "non-responders to corticosteroids".

This is the descriptive study of comparing the prednisolone treatment between the Lille score and pharmacokinetics values in AH patients. Prednisolone treatment have been studied in the patient population with only AH condition. The total serum bilirubin, direct serum bilirubin, indirect bilirubin, ALT, AST, ALP, total protein, albumin, globulin, A/G, creatinine, and urea are all analyzed in the 16 patients. MDF was primarily used to determine the next treatment step based on the severity of alcoholic hepatitis at the outset (28,29). While during the treatment period from Day 1 to Day 7, 4 patients were withdrawn from the studies. Early detection of corticosteroid treatment response is essential for predicting a complicated AH disease and survival, as well as avoiding unnecessary treatment that could worsen the prognosis. As a result, we aimed to compare LM performance at day 1 (LM4) to LM performance at day 7 (LM7) as an earlier predictor of corticosteroid therapy response and survival in patients with SAH. The Lille Model (30), which includes a measurement of response to treatment on day 7 of corticosteroid therapy, can be used to assess improvement (3,30). According to the validated cutoff value >0.45, nearly 40% of patients with SAH are classified as non-responders to corticosteroids, which is associated with a 6-month survival rate as low as 25% and necessitates the discontinuation of prednisolone due to lack of therapeutic benefit. However, this means that LM testing necessarily requires at least 7 days of high-dose corticosteroids and lengthening the hospital stay (31). The Lille model (30), a useful tool in the assessment of liver function improvement in patients receiving corticotherapy, can be used to assess response to therapy (32,33). On Day 7 of corticotherapy, LM is calculated by combining six variables (age, renal insufficiency, albumin, prothrombin time, bilirubin, and evolution of bilirubin at Day 7). Patients are classified as responders to therapy if their LM is less than 0.45 and non-responders if their LM is greater than 0.45. In our study, 6 patients are responders and other 6 patients are non-responders to the prednisolone.

Plasma prednisolone levels were measured at specified time point from 0 to 12 hours’ time period after injection of an oral dose of prednisolone for 12 patients. Peak prednisolone levels were reached 2.5 hours after injection and gradual decrease in level was same in all the patients from the time duration of 0.0 to 12 hours. Earlier studies reported an correlation between the age and prednisolone clearance, suggesting that patient age is an important factor in drug disposition (34). Further the pharmacokinetics study for the responders and non-responders to prednisolone was investigated to know the difference in value of $T_{\text{max}}$, $C_{\text{max}}$, AUC (0–24), AUC(0–∞), $t_{1/2}$, and CL/F (Table 1 & 2). The $C_{\text{max}}$ is known for the amount of time it takes for a drug to reach its maximum concentration (Cmax) after being administrated. Drug absorption and elimination rates determine $T_{\text{max}}$ (35). When taken orally, prednisolone is quickly absorbed. According to a previous study, the time to reach maximum plasma prednisolone concentration (Tmax) in 13 participants using different formulations of 20 mg prednisolone
In our study, both the Tmax and Cmax value was similar in both responders and non-responders. In pharmacology, the area under the curve (AUC) of a drug's plasma concentration versus time after dosage provides information about the drug's exposure and clearance rate from the body. The definite integral of a curve that describes the variation of a drug concentration in blood plasma as a function of time is the area under the curve (AUC) (37,38). Area under the concentration–time curve extrapolated to 24 hours is called AUC (0–24). Area under the concentration–time curve AUC (0–∞) extrapolated to infinity. These are results also clearly shown that no impact was observed in AUC (0–24) and AUC (0–∞) after prednisolone treatment. Prednisolone has a biological half-life (t½) of between 2.1 and 3.5 hours. The mean elimination half-life of prednisolone for responders and non-responders was found to be similar in the current study (38,39). The mean value of pharmacokinetics studies of 12 patients for both the responders and non-responders are mentioned in the Table 3. It was clearly observed that there was not much difference in the responders and non-responders of pharmacokinetics studies. The pharmacokinetics parameters such as Tmax (1), Cmax, AUC (0–24), AUC (0–∞), t½ and CL/F are observed with not much difference. There was no difference in t½ between responders and non-responders. These indicates that prednisolone has impact on Lille score, while no changes were observed in the pharmacokinetics. Interestingly, our findings show that differences in the Lille score of responders and non-responders are not same as in pharmacokinetics studies. Variability in clinical response to corticosteroid therapy could be due to factors other than prednisolone, such as a genetic polymorphism in the gene linked to drug disposition (40). When comparing the Lille score of responders and non-responders significant changes were observed. While in the pharmacokinetics no changes were observed. It may be also worthwhile to correlate pharmacokinetics parameters such as AUC (0–24) and AUC (0–∞) with prednisolone doses. The AUC (0–24) and AUC (0–∞) parameters showed similar value after the prednisolone treatment and no difference was observed between responders and non-responders.

5. Conclusion

In this study, we classified responders and non-responders to prednisolone therapy based on the Lille score after 7 days of treatment. Pharmacokinetic studies included both responders and non-responders to prednisolone therapy, but there was no statistically significant difference between the two groups. These findings imply that pharmacokinetics has no relationship with the ineffectiveness of prednisolone therapy. However, additional cohort and molecular studies may require validating the findings.

Funding
None.

Availability of data and material

The data generated during this study are available from the corresponding author for reasonable requests.

Code availability
Not applicable.

Conflict of interest

The authors have indicated that there are no conflicts of interest associated with the content of this article.

Ethical approval

The studies were approved by the Ethics Committee of the SRM Medical College Hospital and Research Centre (Tamil Nadu, India) (Grant No. 2363/IEC/2021).

Informed consent

Informed consent was obtained from all individual participants included in the study.

Author contributions

Participated in research design: VTM and NRR. Conducted experiments: NRR and RNA. Performed data analysis: NRR. Wrote or contributed to the writing of the manuscript: VKM and NRR.

Consent for publication

Not applicable.

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