MODULATORY ROLE OF SELENIUM AND VITAMIN E AGAINST OXIDATIVE STRESS INDUCED HEPATOTOXICITY AND NEPHROTOXICITY IN RATS EXPOSED SUB-CHRONICALLY TO HEXAVALENT CHROMIUM

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ABSTRACT

Objective: The present study assessed the hepatotoxicity and nephrotoxicity associated with oxidative stress induced by chronic exposure to a very low environmentally relevant dose of hexavalent chromium along with the ameliorative potential of selenium and Vitamin E in male rats.

Methods: Twenty-four male albino rats were divided into four groups. Animals of control group received only distilled water. The treated group received solution of potassium dichromate (K2Cr2O7) at a dose of 1 mg/kg bw/day. The third group received sodium selenate (0.25 mg/kg bw) plus Vitamin E (100 mg/kg bw). The supplemented group received sodium selenate plus Vitamin E along with K2Cr2O7 solution. The animals were treated for 90 consecutive days.

Results: There was a significant decrease in body weight gain and an increase in liver and kidney weight along with an increase in serum glucose, cholesterol, urea, and creatinine; a decrease in protein and albumin levels in the rats treated with K2Cr2O7. The activities of serum enzymes, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, acid phosphatase, and alkaline phosphatase were also increased in treated animals. The activities of enzymes catalase, superoxide dismutase, Gpx and the levels of GSH reduced significantly and level of malondialdehyde increased in K2Cr2O7 treated rats. Liver and kidney tissues exhibited features of toxicity in chromium treated animals. All the effects were reversed in supplemented group.

Conclusion: Chronic exposure to K2Cr2O7 at a very low environmentally relevant dose caused hepatotoxicity and nephrotoxicity induced by oxidative stress in male albino rats; the effects were ameliorated by supplementation with selenium and Vitamin E in combination.

Keywords: Chromium, hepatotoxicity, nephrotoxicity, oxidative stress, selenium, Vitamin E.

INTRODUCTION

Oral exposure to hexavalent chromium (Cr VI) produces gastrointestinal, haematological, hepatic, renal and neurological defects [1]. Exposure to chromium causes damage to liver, the principal organ associated with metabolism, detoxification and secretory function in the body [2]. Long-term chronic exposure to chromium also causes renal injury and produces renal dysfunction [3]. Most of these reports were based on studies with short time exposure at very high exposure doses. However, people are generally exposed to heavy metals including chromium in the environment to a much lower dose and for a longer period. We recently observed an alteration in serum biochemical and hematological parameters in male rats due to chronic exposure to Cr VI at an environmentally relevant dose [4]. Cr VI and its intermediates are capable of generating reactive oxygen species (ROS), leading to oxidative stress. In addition, it reduces the antioxidant capacity by decreasing the activities of different enzyme systems associated with antioxidant defense mechanisms [5]. Chromium is reported to cause both hepatotoxicity and nephrotoxicity through oxidative stress mediated mechanism in experimental animals [6].

In recent times, different antioxidants including natural antioxidants have been evaluated for their ameliorative potential against heavy metal-induced toxicity, including chromium toxicity. Two of the widely studied antioxidants for their role in the amelioration of heavy metal-induced toxicity are micronutrient selenium (Se) and natural antioxidant Vitamin E (Vit E) in combination [7]. Se, an essential micronutrient protects the lipid membrane from oxidative damage caused by peroxidase [8]. Vit E (α-tocopherol) which is located in the cell membrane is one of the most important naturally occurring antioxidants acting against oxidative stress induced by heavy metals including chromium [9]. Recently their roles as antioxidants in combination have been evaluated against many toxicants including chromium [10].

In view of the above fact, the current study aimed to determine the extent of hepatotoxicity and nephrotoxicity produced by a sub-chronic exposure to a very low environmentally relevant dose of hexavalent chromium along with ameliorative potential of selenium and Vitamin E in combination against such chronic exposure.

METHODS

Chemicals
Potassium dichromate (K2Cr2O7) obtained from Mark Specialties Pvt. Ltd. India. Commercial kits for estimation of glucose, total protein, albumin, cholesterol, urea, creatinine, serum glutamate pyruvate transaminase (SGPT) and serum glutamate oxaloacetate transaminase (SGOT) were purchased from the Coral System. Magnesium chloride, sodium hydroxide, sodium-P-nitrophenol, pinitrophenol, citric acid, and sodium citrate were obtained from Sisco Research Laboratories Pvt. Ltd.

Animals
Male albino rats (150–160 g) were used for the study. The animals were obtained from the Committee for the Purpose of Control and Supervision on Experimental Animals, Government of India, registered animal supplier. The animals were maintained in university animal house and were supplied with a standard rat food and water ad
libitum. They were maintained in a controlled condition of temperature (25±2°C) and normal day/night schedule (12L:12D). The Institutional Animal Ethical Committee approval was obtained for the study protocol.

**Study design**

The animals were divided into four groups of six animals in each group. All the animals received their respective treatments orally through gavages for 90 days.

- **Group-I (Control group):** Received distilled water 2 ml/day.
- **Group-II (Chromium treated group):** Received solution of (K₂Cr₂O₇) at a dose of 1 mg/kg body weight/day.
- **Group-III (Selenium plus Vitamin E treated group):** Received sodium selenate (0.25 mg/kg bw) plus Vitamin E (100 mg/kg bw).
- **Group-IV (Supplemented group):** Received sodium selenate (0.25 mg/kg bw) plus Vitamin E (100 mg/kg bw). Along with the solution of K₂Cr₂O₇.

The dose of K₂Cr₂O₇, Se and Vit E were selected on the basis of the previous reports [4,7].

The animals were sacrificed after completion of the treatment period by cervical dislocation under ether anesthesia following Indian Council of Medical Research guide lines [11].

**Body weight and organ weight**

The weight of each animal taken on the 1st day of the experiment was considered as the initial body weight. The body weight taken on the day of sacrifice was considered as final body weight. After autopsy, the liver and kidneys were dissected out and immersed in normal saline and cleared of adherent tissues and blood vessels. The organs were blotted free of mucus, weighed, and expressed per 100 g body weight.

**Blood collection and serum separation**

The blood was collected by cardiac puncture, serum separated, collected and kept at −20°C for future analysis.

**Preparation of liver and kidney homogenate**

The part of liver and kidney tissues were homogenized in aqueous phosphate, K₂PO₄/KH₂PO₄ buffer (0.1 M; pH=7.4); in 4:1 volume of buffer to organ weight at 4°C [12].

**Analysis of serum biochemical parameters**

The serum glucose, total protein, serum albumin, cholesterol, serum urea, creatinine, SGPT and the SGOT enzymes were measured using commercial kits following manufacturers guidelines. The levels of enzymes alkaline phosphatase (ALP) and acid phosphatase (ACP) were estimated by the method of Bessey et al. [13]. Protein from liver and kidney homogenates was estimated by Bradford method [14].

**Assessment of oxidative stress biomarkers**

The level of lipid peroxidation and activity level of various antioxidant enzymes were measured in liver and kidney homogenates using standard methods. The malondialdehyde (MDA) concentration was determined according to the method of Ohkawa et al. [15]. The catalase (CAT) activity was determined according to the method of Aebi [16]. The superoxide dismutase (SOD) activity was determined according to the method of Marklund and Marklund [17]. The glutathione peroxidase activity was determined according to the method of Paglia and Valentine [18]. The reduced glutathione (GSH) level was determined according to the method of Ellman and Fiches [19].

**Histopathological analysis of liver and kidney**

The liver and kidney tissues were sliced in to small pieces and fixed in 4% formalin solution for 48 h. The fixed organs were dehydrated in ascending series of alcohol, cleared in xylene, and embedded in paraffin wax. Then 4–5 μm thick sections of tissues were prepared by rotary microtome and stained by Harris hematoxylin and Eosin. The stained sections were observed under low power (×20) and high power (×40) and photomicrographs were taken for analysis.

**Statistical analysis**

The values were expressed as mean ± SE for comparison between experimental groups. The data with normal distribution and homogeneous variance were analyzed for one-way analysis of variance (ANOVA) and “t” test using statistical software (SPSS 16.0), a p≤0.05 was considered statistically significant.

**RESULTS**

**Effect on body weight gain and organ weight**

There was a significant reduction in percentage gain of body weight after chronic exposure to chromium (1 mg/kg body weight/day) for 90 consecutive days. Weight of both liver and kidney was increased significantly in animals exposed to chromium (Group-II) in comparison to control animals (Group-I). These effects were nearer to control animals in Se and Vit E treated groups (Group-III); and in animals supplemented with Se and Vit E along with chromium (Group-IV) (Table 1).

**Effect on serum biochemical parameter**

There was a significant (p<0.01) increase in the levels of glucose, cholesterol, urea and creatinine and a decrease in levels of protein and albumin in the animals treated with chromium. The serum levels of SGPT and SGOT enzymes were also elevated in these animals. There was a significant increase in activities of enzymes ACP and ALP. Co-treatment with Se and Vit E reversed the conditions (Table 2).

**Effect on histoarchitecture of liver and kidney**

The histological picture of liver in control (Group-I), Se and Vit E treated (Group- III) and supplemented groups (Group – IV) showed normal architecture with several hepatic lobules separated from each other by connective tissue septa housing the portal triad. Each lobule contained well demarked central canal surrounded by radiating cords and separated by blood sinoids. The animals treated with chromium (Group II) showed marked changes in architecture of liver with pronounced vacuolation and fatty degeneration in hepatocytes with congestion of central veins and sinosoids (Fig. 1). Section of kidney in Group-I (control) showed the normal appearance of glomerulus (red arrow), proximal convoluted tubules (yellow arrow), and distal convoluted tubules (green arrow). Group II (chromium treated) showed severe tubular degeneration of proximal convoluted tubules (yellow arrow) and distal convoluted tubules (green arrow), damaged glomeruli (red arrow) and with wide lumina (black arrow). Group III showed improved renal structure such as restoration of glomerulus (red arrow), proximal convoluted tubules (yellow arrow), distal convoluted tubules (green arrow), and narrowing of lumina (black arrow) in the chromium exposed rats. Group III also showed normal renal architecture (Fig. 2).

**Effect on lipid peroxidation**

Levels of MDA increased significantly in both liver and kidney homogenates of chromium treated animals. Supplementation with Se and Vit E reduced chromium induced elevation in MDA levels in both liver and kidney (Tables 3 and 4).

**Effect on antioxidant enzyme system**

There was a significant decrease (p<0.01) in the activities of antioxidant enzymes CAT, SOD, GPx and GSH levels in tissue homogenates of chromium treated animals. The activities of antioxidant enzymes in liver and kidney were found to be restored to control level in supplemented animals (Tables 3 and 4).

**DISCUSSION**

Health hazards associated with exposure to heavy metals have been studied over the years and significant volume of data has been
global problem [1]. For example, people residing near tanneries are subjected to chronic exposure to a very low level of chromium through ground water [20]. Information on health hazards of such low level chronic exposure to chromium is still scarce. Hence, the purpose of the study was to revisit hexavalent chromium (Cr VI) toxicity adopting a protocol simulating chronic oral exposure and to evaluate ameliorating potential of two widely studied antioxidants selenium and Vitamin E against such chronic exposure.

We observed a significant reduction in body weight gain in chromium treated rats. The observation is in a similar line to that of Gilbert et al. who reported long back from their epidemiological study that there was a decrease in net body weight gain in human exposed chronically to chromium [21]. There are reports from many animal studies that confirm our findings of decline in net body weight gain with exposure to chromium [22]. As observed in our study, heavy metal exposures reduce the percentage gain in body weight by mainly reducing the food efficacy [23]. There was a significant increase in weight of liver and kidney in chromium treated rats in our study. This is a common finding in heavy metal induced toxicity as both the organs are associated with metabolism and excretion of toxic substances [24]. Contrary to this, Momo et al. observed that relatively low dose longer exposure to potassium dichromate in rabbit doe did not cause significant change in anatomy of both liver and kidney [25].

Serum biochemical analysis of the study showed an increase in the concentration of glucose, total cholesterol, urea and creatinin levels with a concomitant decrease in total protein and albumin level in chromium treated rats. Both urea and creatinine are routinely evaluated as markers of renal function. Increase in urea and creatinine might be due to the dysfunction of glomerulus, structures associated with renal filtration [26]. An increase in glucose and cholesterol levels in exposed animals might be due to defects in utilization of these nutrients at the tissue level [27]. Chromium is reported to cause increase in cholesterol

accumulated by now on various adverse effects and their mechanisms. Consequent to this, various environmental protection regulations have been promulgated across the nations to protect living organisms against acute exposure to high levels of heavy metals. However, chronic exposure to a lower level of heavy metals through food, water and air is still common in industrial areas and continued to remain as a pertinent exposure to a lower level of heavy metals through food, water and air is still common in industrial areas and continued to remain as a pertinent exposure to a lower level of heavy metals. However, chronic exposure to a lower level of heavy metals through food, water and air is still common in industrial areas and continued to remain as a pertinent exposure to a lower level of heavy metals through food, water and air is still common in industrial areas and continued to remain as a pertinent

Table 1: Effect of selenium (Se) and Vitamin E (Vit E) supplementation on chromium induced changes in body weight gain, daily food consumption and relative weight of liver and kidney

| Parameters                                    | Group I         | Group II        | Group III        | Group IV        |
|-----------------------------------------------|-----------------|-----------------|------------------|-----------------|
| Initial body weight (g)                       | 157.8±2.9       | 162.1±2.3       | 166.6±2.7        | 159.8±3.4       |
| Final body weight (g)                         | 263.5±3.1       | 243.0±5.6       | 278.7±3.0        | 263.4±2.1       |
| Body weight gain (%)                          | 66.98±0.7       | 49.90±0.6a      | 67.22±0.9b##     | 64.76±0.6c#e**f#|
| Food consumption (g/nt/day)                   | 26.3±0.7        | 23.1±0.5a**     | 24.7±0.7b#d*     | 25.1±0.4c#e##f# |
| Weight of liver (g/100g bw)                   | 3.8±0.2         | 4.3±0.1a        | 3.79±0.2b#d*     | 3.95±0.1c#e##f# |
| Weight of Kidney (g/100g bw)                  | 0.5±0.2         | 0.8±0.1        | 0.57±0.02b#d*    | 0.49±0.1c#e#f# |

Group I=Control group; Group II=Chromium treated group; Group III=Se- and Vit E treated group; Group IV=Chromium plus Se- and Vit E supplemented group.

Table 2: Effect of Selenium (Se) and Vitamin E (Vit E) supplementation on chromium induced changes in serum biochemical parameters

| Parameters                                      | Group I        | Group II        | Group III        | Group IV        |
|------------------------------------------------|----------------|-----------------|------------------|-----------------|
| Serum glucose (mg/dl)                           | 103.4±2.0      | 118.5±2.8a**    | 106.6±2.7b#d*    | 109.3±2.1c#e##f#|
| Protein (g/dl)                                  | 6.38±0.1       | 4.73±0.1a**     | 6.89±0.2b#d*     | 7.12±0.2c#e##f# |
| Albumin (mg/dl)                                 | 4.79±0.1       | 3.46±0.1a**     | 4.21±0.1b#d*     | 4.16±0.1c#e##f# |
| Cholesterol (mg/dl)                              | 64.3±2.2       | 74.1±0.9a**     | 65.6±0.5b#d**    | 67.2±1.1c#e##f# |
| Urea (mg/dl)                                    | 42.4±1.1       | 54.29±1.3a**    | 46.7±0.7b#d*     | 44.3±0.8c#e##f# |
| Creatinine (mg/dl)                              | 0.68±0.01      | 1.47±0.5a**     | 0.63±0.04b#d*    | 0.63±0.03c#e##f#|
| SGOT (U/ml)                                     | 61.80±0.4      | 69.40±0.9a      | 64.42±1.0b#d*    | 63.16±1.0c#e##f#|
| SGPT (U/ml)                                     | 52.71±1.2      | 59.28±0.9a      | 53.17±0.9b#d*    | 52.63±0.7c#e##f#|
| ALP (U/ml)                                      | 5.12±0.05      | 7.18±0.05a      | 5.79±0.06b#d*    | 5.96±0.05c#e##f#|
| ACP (U/ml)                                      | 2.16±0.01      | 3.52±0.02a      | 2.73±0.08b#d*    | 2.81±0.05c#e##f#|

Group I=Control group; Group II=Chromium treated group; Group III=Se- and Vit E treated group; Group IV=Chromium plus Se- and Vit E supplemented group.

Values are represented as mean ± SE; animals (n)=6/group. a= Group I versus Group II; b=Group I versus Group III; c=Group I versus Group IV; d= Group II versus Group III; e=Group II versus Group IV; f=Group III versus Group IV; *p<0.05; **p<0.01; ***p<0.001, #=Non significant.

Fig. 1: Represents the histopathological analysis of liver of various groups under chromium treatment and supplementation with selenium plus Vitamin E. Group I-Control; Group II-Chromium treated; Group III-(selenium plus Vitamin E treated); Group IV-(chromium + selenium plus Vitamin E supplemented).

Histopathological examination of liver tissue was carried by hematoxylin and eosin (H and E) staining and the microscopic images were viewed under ×40 magnification (scale bar= 50 µm). CV: Central Vein; S: Sinusoids; black arrows- indicate hepatocytes.
levels in cells by up regulating cholesterol synthesizing enzymes [28]. Contrary to our findings, there are reports that suggest that chromium exposure causes hypoglycemia and this may be due to conversion of hexavalent chromium to trivalent chromium-ATP complex that acts as competitive inhibitor for different ATP-dependent enzymes and several kineses involved in glycolysis [29]. Decline in the total protein and albumin can be associated with generalized reduction in protein metabolism due to general and systemic toxic effects in chromium treated rats [30]. It might be associated with reduced protein synthesis or increased proteolysis or protein degradation [31]. The decline in total protein and glycogen might be associated with generation of oxygen free radical by hexavalent chromium which oxidizes proteins and lipoproteins and impairs liver structure and metabolism [32]. A high level of serum enzymes SGOT and SGPT is indicative of liver injury and is generally associated with exposure to the heavy metal [33]. Both ACP and ALP are the sensitive biomarkers of cellular damage [34].

Cytotoxicity due to chromium exposure is clearly indicated by histopathological alterations in hepatic and renal tissues in our study. Deterioration of organization of hepatic cords with disruption of endothelial lining in sinusoids and central veins in liver sections of chromium exposed animals are indicators of hepatotoxicity [2]. Similarly, microscopic examination of kidney tissue treated with potassium dichromate showed signs of degeneration in tubular epithelial cells in form of vacuolation, congested glomerular capillaries and glomerular tufts, signs of chromium induced nephrotoxicity [3].

Disruption of serum biochemical profile specially the levels of toxicological marker enzymes suggested that chronic exposure to chromium might have generated ROS, thus causing oxidative stress leading to both hepatotoxicity and nephrotoxicity. The assumption is supported by our observation of changes in oxidative biomarkers which are the indicators of tissue’s ability to cope with oxidative stress [35]. There was a significant increase in MDA levels in both liver and kidney of chromium treated rats. MDA is a major oxidation product of peroxidized polyunsaturated fatty acids and an increased MDA content is an indicator of membrane lipid peroxidation [36]. Several studies have reported elevation of MDA in both kidney and liver tissues following chromium exposure. Along with elevation of MDA, we observed decline in activities of antioxidant enzymes in chromium exposed animals, which might be due to loss of cells expressing these enzymes due to direct inhibitory actions of ROS on these enzymes. Our results revealed that sub-chronic exposure to chromium caused a statistically significant decline in both CAT and SOD in liver and kidney of exposed animals. CAT/SOD provides the first line of defense system against oxygen toxicity [37]. The decline in SOD activity may lead to massive production of superoxide anions for conversion of superoxide to water, because this dismutation reaction is catalyzed by SOD. CAT, on the other hand, is responsible for catalytic decomposition of hydrogen peroxide to molecular oxygen and water [38]. Similarly GPx and GSH are also important sensitive indicators of increased oxidative stress. GPx modifies peroxide to nontoxic hydroxyl compound to protect the cell membrane structure. GSH is normally present in millimolar concentrations in cells and is known to protect the cellular system against the toxic effects of lipid peroxidation.

Table 3: Effect of selenium (Se) and Vitamin E (Vit E) supplementation on chromium-induced changes in oxidative stress parameters in liver

| Parameters | Group I | Group II | Group III | Group IV |
|------------|---------|----------|-----------|----------|
| CAT (µmol H₂O consumed/min/mg protein) | 31.53±0.127 | 26.318±0.231a | 29.89±0.316b | 30.17±0.341c|
| SOD (µmol/mg protein) | 5.891±0.234 | 4.116±0.211a | 5.610±0.208b | 5.192±0.209c|
| GSH (µmol/mg protein) | 2.117±0.166 | 1.023±0.130a | 1.938±0.210b | 1.829±0.307c|
| GPx (Unit/mg protein) | 38.93±0.216 | 35.130±0.249a | 37.82±0.317b | 37.92±0.217c|
| MDA (nmol/mg protein) | 3.176±0.306 | 4.863±0.230a | 3.762±0.412b | 3.496±0.315c|

Group I=Control group; Group II=Chromium treated group; Group III=Se- and Vit E treated group; Group IV=Chromium plus Se- and Vit E supplemented group. Values are represented as mean ± SE; animals (n)=6/group. a=Group I versus Group II; b=Group I versus Group III; c=Group I versus Group IV; d=Group II versus Group III; e=Group II versus Group IV; f=Group III versus Group IV; ***p<0.001; ***p<0.001; # Non significant. CAT: Catalase, SOD: Superoxide dismutase, GSH: Reduced glutathione, GPx: Glutathione peroxidase, MDA: Malondialdehyde

Table 4: Effect of selenium (Se) and Vitamin E (Vit E) supplementation on chromium-induced changes in oxidative stress parameters in kidney

| Parameters | Group I | Group II | Group III | Group IV |
|------------|---------|----------|-----------|----------|
| CAT (µmol H₂O consumed/min/mg protein) | 18.87±0.218 | 11.22±0.340a | 16.83±0.632b | 16.97±0.718c|
| SOD (µmol/mg protein) | 1.62±0.196 | 1.241±0.149a | 1.44±0.152b | 1.39±0.124c|
| GSH (µmol/mg protein) | 1.88±0.264 | 1.156±0.118a | 1.53±0.139b | 1.69±0.133c|
| GPx (Unit/mg protein) | 9.37±0.217 | 6.835±0.426a | 7.48±0.273b | 7.78±0.163c|
| MDA (nmol/mg protein) | 21.62±0.148 | 23.48±0.173a | 22.79±0.212b | 22.59±0.173c|

Group I=Control group; Group II=Chromium treated group; Group III=Se- and Vit E treated group; Group IV=Chromium plus Se- and Vit E supplemented group. Values are represented as mean ± SE; animals (n)=6/group. a=Group I versus Group II; b=Group I versus Group III; c=Group I versus Group IV; d=Group II versus Group III; e=Group II versus Group IV; f=Group III versus Group IV; **p<0.01; ***p<0.001; # Non significant. CAT: Catalase, SOD: Superoxide dismutase, GSH: Reduced glutathione, GPx: Glutathione peroxidase, MDA: Malondialdehyde
It is very important in maintaining cellular redox status and its depletion is considered as a marker of oxidative stress [39]. Oxidative stress in tissue may cause oxidative catabolic effects leading to lipid peroxidation accompanied with the depletion of tissue GSH [40]. Our results on oxidative stress parameters in liver and kidney of chromium exposed animals are supported by previous findings on heavy metal induced oxidative stress. A significant increase in MDA level and a significant decrease in CAT-SOD system and GPx-GSH activity is a clear indication of oxidative stress, which might have caused functional and structural disruption in both liver and kidney of chromium exposed animals. This is further confirmed by our biochemical and histopathological analysis of these tissues. All these changes in biochemical, histo pathological and oxidative stress parameters observed in animals exposed chronically to chromium were found to be reversed when chromium was supplemented with selenium and Vitamin E in combination. The choice of these two micronutrients for supplementation along with chromium was based on success of these antioxidants against various chemical induced oxidative stress [41]. It is now established that they complement each other in their function as antioxidants and prevent production of free radicals and neutralize them. Therefore, both selenium and Vitamin E have got great potential as emerging antioxidant therapy against heavy metal induced toxicity in general and against chromium in particular.

CONCLUSION

Our present study clearly demonstrated that chronic exposure to a environmentally relevant low dose of chromium can cause both hepatotoxicity and nephrotoxicity induced by oxidative stress; and both selenium and Vitamin E in combination, can mitigate the deleterious effects of chromium on liver and kidney.

AUTHOR’S CONTRIBUTION

SC, JS, and SD contributed to data accusation, analysis of parameters, data analysis, and statistical analysis. SC prepared the initial version of the manuscript with inputs from JS and SD. DC contributed to initial study design and data accusation, statistical analysis, drafted the initial version of the manuscript and contributed to its critical revision and preparation of final version in consultation with all the contributing authors.

COMPETING INTEREST

The authors declare that they have no conflicts of interest.

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