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RESEARCH ARTICLE

TO EVALUATE THE EFFICACY AND SAFETY OF ZINC AS AN ADD ON THERAPY TO PREDNISOLONE FOR PRODUCING EARLY REMISSION OF PEDIATRIC NEPHROTIC SYNDROME : A RANDOMIZED CONTROLLED TRIAL

Alok Kaushik, Garima Bhutani, Manoj Rawal, Renu Garg, Seema Rani and Rahul Saini

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Key words:-
Pediatric Nephrotic syndrome,zinc, urinary protein creatinine ratio, Prednisolone,

Abstract

Introduction: Nephrotic syndrome is a common pediatric kidney disorder characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Zinc deficiency is common due to urinary losses and may delay recovery. This study evaluated the efficacy and safety of zinc as an adjunct to prednisolone in achieving early remission.

Materials and Methods: A prospective, open-label, randomized comparative study was conducted in 62 children (1–15 years) with first-episode nephrotic syndrome. Patients received either prednisolone plus zinc (n=31) or prednisolone alone (n=31). Urinary protein, urinary protein-creatinine ratio, urine output, fluid intake, body weight, abdominal girth, and blood pressure were monitored daily. Serum electrolytes (Na^+, K^+), total protein, albumin, globulin, A:G ratio, lipid profile, serum creatinine, and serum urea were measured at baseline and at remission.

Results: Zinc significantly shortened time to remission (9.37±1.17 vs. 11.77±2.08 days; $p<0.001$) and produced greater improvement in proteinuria, UPCR, urine output, edema, and body weight. Biochemical parameters improved significantly in both groups without significant intergroup differences. No serious adverse events occurred.

Conclusion: Zinc is a safe, inexpensive, and effective adjunct to prednisolone that accelerates remission in pediatric nephrotic syndrome.

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Introduction:-

Nephrotic syndrome is a disorder of the kidney that is defined by the presence of > 3 to 3.5 g per day of proteinuria, which results in hypoalbuminemia, edema, and hyperlipidemia. Nephrotic syndrome occurs due to a disruption of the glomerular filtration barrier. The estimated prevalence of nephrotic syndrome is around 16 cases per 1,00,000 children.[1] Nephrotic syndrome is more common in boys than girls at younger ages, but once adolescence is reached, there is no significant difference between genders. Increased incidence and more severe diseases are seen in African American and Hispanic populations.[1] Steroid therapy remains the first-line treatment for nephrotic syndrome, and the majority of children achieve remission with corticosteroids. However, a subset of patients does not respond to steroids even after adequate treatment. These patients are categorized as having Steroid-Resistant Nephrotic

Corresponding Author:-Alok Kaushik

Syndrome (SRNS). SRNS is associated with poor prognosis because persistent proteinuria can progressively damage renal tissues and increase the risk of chronic kidney disease.[2]

Zinc is an essential trace element required for normal growth, immune function, protein synthesis, cellular differentiation, and tissue repair. It acts as a cofactor for numerous enzymes and plays an important role in maintaining the structural integrity of cells.[3] Zinc deficiency affects multiple organ systems including the skin, gastrointestinal tract, immune system, central nervous system, musculoskeletal system, and reproductive organs. In children, zinc deficiency can impair growth, reduce immunity, and increase susceptibility to infections.[4] Low serum zinc levels have frequently been reported in children with nephrotic syndrome. Zinc deficiency in children may occur due to inadequate dietary intake, impaired intestinal absorption, increased urinary loss or gastrointestinal losses associated with diarrhea.[5]Since nephrotic syndrome involves heavy protein loss through urine, important micronutrients bound to proteins, including zinc, may also be lost and zinc supplementation can reduce morbidity and mortality specially among children due to gastrointestinal and respiratory disease.[6]So,this study had been conducted to know whether the zinc also have any role in hastening the remission of nephrotic syndrome.

Materials and Methods:-

This prospective, open-label, randomized, comparative clinical study was conducted in Department of Pharmacology in colloboration with Department with Pediatrics and Department of Biochemistry.at B.P.S Govt Medical College for women, Khanpur Kalan, Sonipat.The study was started after getting approval from the university and the institutional ethical committee. Children aged 1–15 years presenting with the first episode of nephrotic syndrome and whose parents/guardians provided written informed consent were included in the study. In addition oral assesnt was taken from children aged 7-11 years and written assent was taken from older children. Children with malabsorption, malnutrition, hepatic disorders, chronic illnesses such as tuberculosis, secondary nephrotic syndrome, or refusal of consent were excluded. Of the 70 patients screened, 65 met the eligibility criteria and were randomized into Group A (n=33) and Group B (n=32) using computer-generated randomization. Three patients were lost to follow-up, and 62 patients completed the study.All patients underwent detailed history taking, physical examination, and relevant investigations at enrollment. Complete blood count, Mantoux test, and chest X-ray were performed to exclude active tuberculosis. All findings were recorded in a case record form.

Both groups received standard steroid therapy with prednisolone 2 mg/kg/day (maximum 60 mg) for 6 weeks, followed by 1.5 mg/kg on alternate days for the next 6 weeks. In addition, Group A patients received zinc syrup 20 mg/day for 14 days or until remission, whichever was longer, while Group B did not receive zinc supplementation. All participants were advised dietary modifications including salt restriction, high-protein and high-fiber diet, and avoidance of high-fat foods. Patients were hospitalized and treated according to their allocated group until remission. Body weight, blood pressure, fluid intake, urinary protein, spot urinary protein-creatinine ratio, 24-hour urine output, and abdominal girth were assessed daily from baseline till 14 days or until the day of remission which ever was longer. Serum protein, albumin, globulin, A:G ratio, cholesterol, creatinine, urea and electrolyte were assessed at baseline and at day of remission. Patients were monitored for remission and other complications of nephrotic syndrome. Remission was defined as nil or trace urinary protein for three consecutive early morning urine specimens. The primary outcome measure was remission of nephrotic syndrome, while secondary outcomes included comparison of renal parameters between the two groups.

Statistical Analysis:-

All the collected data was entered into a Microsoft Excel sheet and analyzed using SPSS version 26. Quantitative data were expressed as Mean ± SD. Intragroup comparison was done using repeated measure ANOVA followed by post hoc Bonferroni test and paired t-test, while intergroup comparison was performed using independent t-test. Chi-square test was used for comparison of sex distribution between the groups. A p-value <0.05 was considered statistically significant.

Results:-

Demographic profile of study participants:-

Outof a totalof 62 patient, 31 underwent steroid therapy with zinc supplementation (Group A) while remaining 31 underwent steroid therapy alone without zinc supplementation (Group B).The mean age of the patients in both groups was comparable - 5.00 ± 3.29 years in group A and 5.52 ± 3.02 years in group B.In group A, there were 18 male patients and 13 female patients where as in group B,there were 12 male patients and 19 female patients.

Efficacy Assessment:-

Urinary protein assessment:-

Urinary protein was assessed by dipstick method.The mean urinary protein values of both the groups is shown in table 1.Intergroup comparison demonstrated significantly lower urinary protein levels in Group A compared to Group B on Day 10 ($p < 0.05$) and a highly significant difference on Days 6–9, 12, and 14 ($p < 0.001$).

Urinary Protein Creatinine Ratio (UPCR) Assessment:-

Mean urinary protein creatinine ratio (UPCR) values of both the groups is shown in table 1. Intergroup analysis demonstrated a highly significantly lower urinary protein creatinine value in group A as compared to group B on days 7-14 ($p < 0.001$).

24 Hour Urine Output (mL) Assessment:-

Mean 24 hr urine output values of both the groups are shown in table 1. Intergroup comparison demonstrated significantly greater values in group A on days 7 and 12 and highly significantly greater values on days 5,6, 9-11,13 and 14. ($p <0.001$

Fluid Intake:-

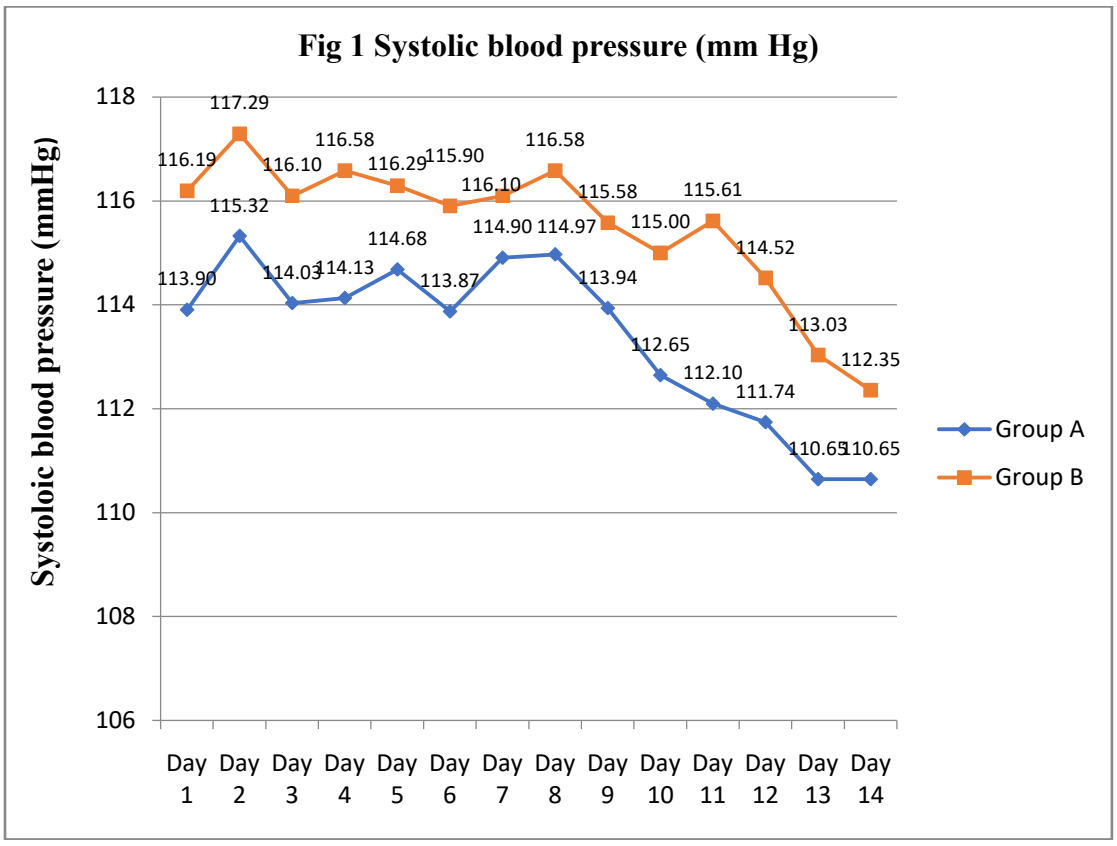
The mean fluid intake values of both the groups is shown in table 1. Intergroup analysis show that these value were significantly greater ($p<0.05$) on days 6 and 7 and highly significant greater on days 10-14 in group A ($p <0.001$) .

Abdominal Girth:-

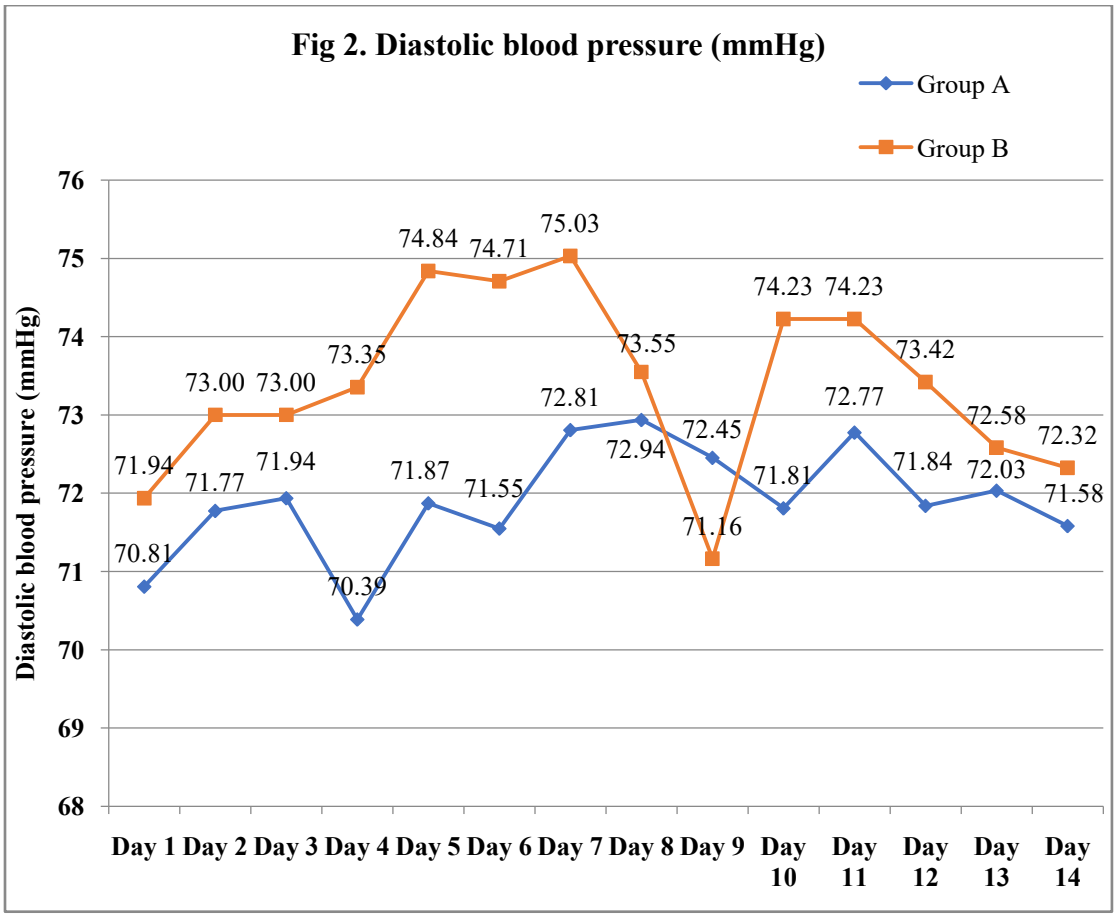
The mean abdominal girth values of both the group is shown in table 2. Intergroup analysis show that these values were significantly greater on days 7 and 13 ($p < 0.05$) and highly significantly greater on days 8–12 ($p < 0.001$) in group A.

Body weight:-

The mean body weight values of both the groups is shown in table 2. Intergroup analysis show that these values were highly significantly greater in group A as compared to group B on days 8–11 ($p < 0.05$).



Blood pressure (mmHg):-
As shown in figure 1, significantly changes in systolic BP values with respective baseline were noted in Group A on Days 13 and 14 ($p < 0.05$), while Group B showed significant change on Day 12 ($p < 0.05$) and highly significant changes on Days 13 and 14 ($p < 0.001$). Intergroup analysis demonstrated significant difference on Day 10 ($p < 0.05$) and highly significant differences on Days 11 and 12 ($p < 0.001$). However,fig 2 depicts that as compared to baseline, diastolic blood pressure showed no significant difference in Group A throughout study period, while Group B showed significant changes on Days 5–7 ($p < 0.05$). Intergroup analysis revealed no statistically significant difference between the groups throughout the study period.



Time to Remission:-
Time taken to attain remission was calculated in all patients in both the groups.It was 9.37±1.17days in groupAand 11.77±2.08 days in group B. This difference was statistically highly significant .

9.Serum electrolytes (Na^+, K^+), total proteins, serum albumin, serum globulin, A:G ratio, lipid profile (total cholesterol, triglycerides, LDL, VLDL, HDL), serum creatinine, and serum urea were assessed at baseline and on the day of remission. All these parameters showed highly statistically significant difference on day of remission as compared to baseline values in both groups But intergroups analysis showed no statistically significant difference at any point of study.

Safety Assessment:-
Safety assessment was carried out in both groups from Day 1 to Day 14 or day of remission which ever was longer. Side effects was noted by taking history and doing physical examination in each patient. During the entire period, all patients were closely monitored for systemic side effects. Side effects were mild and there was no serious side effect observed in both groups.

Discussions:-

There is paucity of literature regarding remission in nephrotic syndrome on zinc therapy. We were able to find only few studies showing effect of zinc on nephrotic syndrome.Kumaret al. observed an earlier decline in heavy dipstick proteinuria (3+ to 4+) among zinc-treated children. Despite similar baseline severity in our study , the zinc group demonstrated a faster shift to trace or negative readings, underscoring zinc's ability to enhance steroid responsiveness and accelerate remission.[6] Comparable evidence from Nardini et al. who defined remission based on the first negative or trace dipstick value, further supports this pattern of early response.[7] The earlier remission in our zinc group, despite equal baseline proteinuria, reinforces that the improvement is attributable to zinc therapy.

The beneficial effect of zinc on reducing the urinary protein–creatinine ratio (UPCR) is strongly supported by Ghafoorimehr et al. who reported a baseline urinary protein creatinine ratio of 12.67 ±8.87 mg/mg**,** indicating substantial proteinuria in steroid-sensitive nephrotic syndrome. In our study, the zinc-supplemented group showed a clearly faster decline in urinary protein creatinine ratio than the control group, reflecting quicker restoration of glomerular permeability.Iyengar et al.showed that urinary protein creatinine ratio values in infrequent-relapse was11 ± 5.5 mg/mg**,** frequent relapses was8 ± 3.1 mg/mg**,** and in steroid-resistant cases was approximately 12 ± 4.8mg/mg.[1]

The beneficial effect of zinc on 24-hour urine output is strongly supported by our findings and is consistent with the observations of Dinesh Kumar et al. who reported that children receiving zinc therapy demonstrated an earlier and more pronounced increase in urine output compared with those on standard therapy alone. The beneficial effect of zinc on reducing edema-related body weight is strongly supported by our findings and aligns with the observations of Nardini et al. who reported a median body-weight Standard deviation score of 0.39 (range –2 to +3), suggesting that most children presented with normal to mildly elevated weight due to edema an observation consistent with the baseline fluid overload seen in our cohort.[7] The study by Dinesh Kumar et al. demonstrated that zinc therapy is safe and does not adversely affect blood pressure in children with nephrotic syndrome. Our findings are consistent with this observation, as both systolic and diastolic blood pressure remained stable throughout treatment in the zinc-supplemented group. So, all of these studies supported our study that zinc therapy in nephrotic syndrome leads to early remissions.

Strength:-

Strength of present study is our pin point approach to see the effect of zinc on remission of nephrotic syndrome in paucity of studies andliterature.Another important strength is the focused evaluation of zinc supplementation, which is affordable, safe, easy to administer, and associated with minimal side effects, supporting its potential use in routine clinical practice.

Limitation:-

Limitations of the study were small sample size, open-label design, short follow-up duration, and inclusion of only pediatric patients, which may limit generalizability. Lack of blinding and loss to follow-up in a few patients may also have introduced bias.

Summary:-

This is a prospective, open-labelled, randomized comparative study which evaluated the efficacy and safety of zinc as an adjunct to prednisolone in 62 children with first-episode nephrotic syndrome. Zinc supplementation significantly shortened the time to remission and produced earlier improvement in proteinuria, urinary protein-creatinine ratio, 24-hour urine output, edema, and body weight compared with prednisolone alone. Secondary biochemical parameters, including serum proteins, lipid profile, serum electrolytes, serum urea, and serum creatinine, improved significantly from baseline in both groups without significant intergroup differences. Zinc was well tolerated, with no serious adverse events, supporting its role as a safe, inexpensive, and effective adjunct for achieving earlier remission in pediatric nephrotic syndrome.

Conclusion:-

Our study concluded that Zinc administration along with standard steroid therapy is effective in early remission in pediatric nephrotic syndrome.

Table 1 – Mean values of urinary protein,urinary protein creatinine ratio,24 hour urine output and fluid intake in both the group.

Parameters	Group	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day	9th day	10th day	11th day	12th day	13th day	14th day
Urinary Protein(0/1/2/3)	A	3.03 ± 0.18	3.00± 0.00	3.13± 0.34 ##	2.45± 0.81 ##	2.10± 0.91 ##	1.23± 1.06 ##	0.55± 0.81 ##	0.19± 0.54 ##	0.26± 0.44 ##	0.26± 0.44 ##	0.45± 0.51##	0.74± 0.51##	0.65± 0.55 ##	0.87± 0.50 ##
	B	3.10 ± 0.30	3.10± 0.30	3.16± 0.52	2.74± 0.73 #	2.65± 0.61 ##	2.19± 0.91##	1.90±1 .19 ##	1.52±1 .12 ##	1.16± 1.10 ##	0.81± 0.91 ##	0.48± 0.57 ##	0.16± 0.37 ##	0.45± 0.51 ##	0.32± 0.54 ##
Urinary protein creatinine ratio(mg/mmol)	A	337.03 ±24.04	330.90± 17.82 #	329.00± 19.19 #	316.68± 19.06 ##	311.74 ± 26.53 ##	272.61 ± 47.12 ##	214.13 ± 58.23 ##	158.00 ± 61.95 ##	120.45± 52.24 ##	97.90 ± 26.14 #	90.32 ± 16.22 #	85.90 ± 14.00 #	82.48 ± 11.76 #	79.58± 11.03 #
	B	336.00 ±26.63	327.94± 19.41 #	328.74± 15.72 #	324.06± 10.83 #	306.42 ± 25.89 ##	293.84 ± 28.80 ##	273.90 ± 43.61 ##	243.61 ± 67.36 ##	204.23± 70.65 ##	173.19± 67.91 ##	153.77± 65.61 ##	137.61± 58.65 ##	111.39± 20.08 #	98.39± 10.37 #
24 hour urine output (ml)	A	477.42 ± 22.90	496.45 ± 21.67	505.16 ± 22.72	514.68 ± 18.14 ##	538.39 ± 19.45	567.29 ± 17.93 #	627.10 ± 20.07 #	697.10 ± 20.08 ##	745.65 ± 17.90 ##	780.65 ± 18.44 ##	785.29 ± 17.37 ##	800± 18.16 ##	850.45 ± 18.22 ##	880.00 ± 18.14 ##
	B	470± 34.96	480± 29.55	500± 31.74	504± 18.77 ##	510 ± 25.82	540 ± 29.63 #	600 ± 23.99 #	650.00 ± 29.22 ##	700.20 ± 29.45 ##	720.00 ± 32.10 ##	740.00 ± 30.23 #	760.65 ± 27.43 ##	800.04 ± 22.23 #	820.06 ± 18.77 #
Fluid intake (ml)	A	325.48 ± 4.97	358.06 ± 9.85 #	359.03 ± 6.92#	362.58 ± 7.03 ##	405.81 ± 11.5 ##	440.00 ± 11.7 ##	479.68 ± 11.2 ##	518.06 ± 16.5 ##	547.10 ± 16.1 ##	585.32 ± 31.2 ##	600.10 ± 51.3 ##	650.19 ± 55.3 #	700.94 ± 60.34 ##	750.00 ± 65.35 ##
	B	322.03 ± 37.1	352.7 ± 31.93	357.74 ± 30.2	360.00 ± 29.23	400 ± 28.64	420 ± 40.13 #	460 ± 48.88 #	510 ± 43.35 ##	530± 43.55 ##	540± 40.97 #	550.03 ± 56.98 #	600.94 ± 32.11 #	650± 49.51 #	700±51.27 ##

 # Indicates significant difference as compared to baseline within the same group (p < 0.05). ##Indicates highly significant difference as compared to baseline within the same group (p < 0.001).

Table 2- Mean values of abdominal girth andBody weight of both the groups.

Parameters	Groups	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day	9th day	10th day	11th day	12th day	13th day	14th day
Abdominal girth (cm)	A	60.00 ± 5.94	59.84 ± 4.88	58.71 ± 5.54 #	57.61 ± 5.04 #	56.55 ± 4.82 ##	55.27 ± 4.79 ##	54.19 ± 4.05 ##	52.42 ± 3.00 ##	51.35 ± 2.83 ##	50.40 ± 2.66 ##	49.73 ± 2.84 ##	49.44 ± 2.72 ##	49.07 ± 2.73 ##	48.73 ± 2.86 ##
	B	60.77 ± 5.95	60.37 ± 5.45	59.29 ± 5.14 #	59.23 ± 4.37 #	58.58 ± 3.85 #	58.35 ± 4.85 #	58.35 ± 4.85 #	56.45 ± 4.03 ##	56.06 ± 4.07 ##	54.95 ± 3.86 ##	53.84 ± 3.70 ##	52.52 ± 3.65 ##	51.56 ± 3.74 ##	50.48 ± 3.89 ##
Body weight (kg)	A	23.29 ± 10.88	23.03 ± 10.45	22.71 ± 10.35	22.00 ± 9.79 ##	21.16 ± 9.21 ##	20.39 ± 8.53 ##	19.96 ± 8.41 ##	19.42 ± 8.05 ##	19.13 ± 7.52 ##	18.88 ± 7.48 ##	18.76 ± 7.33 ##	18.93 ± 7.37 ##	18.96 ± 7.40 ##	18.84 ± 7.36 ##
	B	27.68 ± 9.13	27.61 ± 8.85	27.39 ± 8.80	27.10 ± 8.86 #	26.39 ± 8.35 #	25.87 ± 8.03 ##	25.29 ± 7.57 ##	25.32 ± 7.63 ##	24.84 ± 7.51 ##	24.58 ± 7.55 ##	24.22 ± 7.29 ##	23.80 ± 7.30 ##	23.56 ± 7.50 ##	23.44 ± 7.55 ##

 # Indicates significant difference as compared to baseline within the same group ($p < 0.05$). ## Indicates highly significant difference as compared to baseline within the same group ($p < 0.001$).

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