Safety and Effectiveness of High-Dose Vitamin C in Patients with COVID-19; A Randomized Controlled open-label Clinical Trial

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Abstract

Background: To assess the effectiveness of vitamin C treatment against coronavirus disease 2019 (COVID-19)

Methods: An open-label, randomized, and controlled trial was conducted on patients with severe COVID-19 infection. The case and control treatment groups each consisted of 30 patients. The control group received lopinavir/ritonavir and hydroxychloroquine and the case group received high-dose of vitamin C (six gr daily) added to the same regimen.

Results: There were no statistically significant differences between two groups with respect to age and gender, laboratory results, and underlying diseases. On the 3rd day of hospitalization, the mean core body temperatures was significantly lower and SpO2 was higher In the case group (p value = 0.001, and 0.014, respectively). The median length of hospitalization in case group which was significantly longer than the control group (8.5 days *vs.* 6.5 days) (p value = 0.0280). There was no significant difference in SpO2 levels at discharge time, the length of ICU stay, and mortality between the two groups.

Conclusions: We did not find significantly better outcomes in the group who were treated with high-dose vitamin C in addition to the main treatment regimen at discharge.

Trial registration: The project was registered by Iranian Registry of Clinical Trials.

IRCT20200411047025N1

Introduction

The coronavirus disease 2019 (COVID-19) pandemic which started at late 2019 and spread the world outrageously is caused by infection with Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the coronaviridae family. By September 2020, almost one million lives have been sacrificed by this disease, even more deaths are expected unless proper management does not take into place soon, in terms of prevention, transmission, and treatment. Ascorbic acid or Ascorbate (vitamin C) is an essential water soluble nutrient that functions as a key antioxidant and is involved in the synthesis of collagen and neurotransmitters, and affects wound healing, energy metabolism, nervous system function, and immune cell health [1–3]. The serum level of this vitamin has been correlated with its effect on the endothelial function [4], cellular immune function [5], anti-oxidative capacity, neutrophil function [6], and treatment of cancer and pancreatitis [7, 8]. Intravenous (IV) administration increases the plasma ascorbate concentrations more than oral supplementation (30 mM vs 0.2 mM, respectively) [9, 10].

The evidence behind theoretical possible effect of vitamin C against COVID-19 is promising. In a clinical study of the role of ascorbic acid against Ebstein Barr Virus (EBV) infection showed the EBV IgG and IgM antibody levels reduced during IV vitamin C therapy [11]. Also in a case report of enterovirus/rhinovirus induced acute respiratory distress syndrome (ARDS) in 2017, infusion of high-dose IV vitamin C was associated with rapid resolution of lung injury [12]. The impact of vitamin C administration on alleviating lung injury has also been investigated and supported in other studies [13]. There are other studies expressing the positive effect of IV vitamin C on patients with severe sepsis [14–16]. A meta-analysis also reported the impact of vitamin C on decreasing the duration of ICU-admission and mechanical ventilation care in patients with ARDS [17–19].

Since the impact of IV vitamin C observed on the treatment of viral-induced ARDS and the important role of this vitamin on the immune and endothelial system, we aimed to investigate the correlation of the high-dose IV vitamin C administration with improvement of 2019-nCoV-induced ARDS. There is lack of data and clinical trials which studied this correlation recently.

Materials And Methods

Participants

Between April and May 2020, 85 patients with compelling clinical symptoms for diagnosis of COVID-19 were admitted to Ziaeian Hospital, Tehran, Iran. Based on the eligibility criteria (Fig. 1), 25 patients were excluded and 60 patients were included in the study. The inclusion criteria were age older than 18 years, positive COVID-19 polymerase chain reaction (PCR) test or COVID-19 suspicion based on clinical findings (mainly fever, dyspnea, dry cough), imaging findings of COVID-19 on spiral chest computer tomography (CT) or high resolution CT (HRCT) imagings validated by a trained radiologist, clinical manifestations of ARDS or myocarditis, and oxygen saturation lower than 93% from admission or after 48 hours from the first COVID-19 treatment. The exclusion criteria were receiving anti-retroviral therapy or immune system booster medications in the last three months, no proven and confirmed COVID-19 disease based on the inclusion criteria, patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency, patients with end stage renal diseases (ESRD), and pregnancy.

Study arms and treatment plans

The patients were divided into two subgroups equally by block randomization; the case group included 30 patients receiving 1.5 grams vitamin C IV every six hours for five days and the control group included 30 patients who did not receive vitamin C. All of the participants were also treated with oral Lopinavir/Ritonavir (Kaletra, Abbott Laboratories) 400/100 mg twice daily and daily dose of oral Hydroxychloroquine (400 mg) according to the Iranian COVID-19 treatment protocol at time of this study (it should be noted that based on the vast number of studies for COVID-19, hydroxychloroquine is not considered as mainstay in the protocol for COVID-19 in Iran). On the first day of hospitalization, laboratory studies including complete blood count (CBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were obtained. Patients were assessed by daily measurements of core body temperature, respiratory rate (RR), heart rate (HR), and peripheral capillary oxygen saturations (SpO2). The treatment subsided whenever any kind of drug side effects

appeared. Some of the patients deteriorated during the admission and received corticosteroid (methylprednisolone 125 mg daily for three days) and IVIG (5 to 10 gr daily for three to five days). Patients were discharged when they achieved a stable SpO2 > 92%, no evidence of respiratory distress was remaining, and were afebrile for at least three consecutive days.

Sample size calculation was performed for non-inferiority tests of difference between two group proportions. We assumed an effectiveness of 65% for the intervention group and effectiveness of

50% for the control group. We also assumed a margin of noninferiority of at least 10% between the two groups. The power of the study was determined as 90% (G∗Power, Erdfelder, Faul, & Buchner, 1996).

Ethical considerations

In accordance to the declaration of Helsinki, written informed consent was obtained from all participants before initiation of the study. The patients were assured that declining to participate in the study or leaving the study at any point would not affect the quality of their treatment and that they would thereafter receive the standard care. The study protocol was approved by the institutional review board (IRB) of Tehran University of Medical Sciences (TUMS) with Ethical code (IR.TUMS.VCR.REC.1399.078).

Measurements and statistical analysis

In this open label and nonblinded study, distribution of age, gender, initial clinical symptoms, and vital signs of the first day of admission were compared between the two groups. The vital signs including body temperature, RR, HR and SpO2 were also compared on the 3rd and last day of treatment between the two groups as an outcome measure. Differences in duration of hospitalization, number of patients whose condition deteriorated and needed ICU admission, length of ICU admission, and difference between mortality rates were measured.

Data was analyzed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Quantitative variables are reported by mean and standard deviation (SD) and qualitative variables are reported using frequency and percentage. Because of the normal distribution of our data via Shapiro-Wilk test, the independent t-test was used to assess the means differences and a mixed-design analysis of variance model (ANOVA) was performed to evaluate the effect of time on body temperature. Chi-square and Fisher's exact tests were used to assess the statistical relationships between categorical variables. The level of significance was set as P-value < 0.05 for all analyses.

Results

Demographic characteristics, underlying diseases, and clinical and laboratory findings

Demographic characteristics, underlying diseases, and clinical and laboratory findings are presented in Table 1. Male to female ratio was 1:1. There were no statistically significant differences between two groups considering age and gender, laboratory results and underlying diseases (p value > 0.05). All clinical findings except for fever (23.33% *vs.* 63.33% in case and control groups, respectively, p value = 0.002) and myalgia (13.33% *vs.* 60.0% in case and control groups, respectively, p value < 0.001)were not significantly different between the two groups.

Table 1
Demographics characteristics, underlying diseases, and clinical and laboratory findings and outcomes

		Group		
		Case (n = 30)	Control (n = 30)	P value
Age(year), mean (SD)		57.53(18.27)	61(15.90)	0.436
Sex, n (%)	Female	15(50.00%)	15(50.00%)	> 0.9
	Male	15(50.00%)	15(50.00%)	
Hypertension, n(%)		15(50.00%)	10(33.33%)	0.190
Diabetes mellitus, n(%)		12(40.00%)	11(36.67%)	0.791
Ischemic heart disease, n(%)		4(13.33%)	7(23.33%)	0.506
COPD, n(%)		3(30.00%)	3(30.00%)	> 0.9
Thyroid disease, n(%)		2(6.67%)	3(30.00%)	> 0.9
Fever, n(%)		7(23.33%)	19(63.33%)	0.002
Chill, n(%)		7(23.33%)	9(30.00%)	0.559
Dyspnea, n(%)		25(83.33%)	21(70.00%)	0.222
Myalgia, n(%)		4(13.33%)	18(60.00%)	< 0.001
Weakness, n(%)		2(6.67%)	4(13.33%)	0.671
Cough, n(%)		26(86.67%)	23(76.67%)	0.506
Sputum, n(%)		1(3.33%)	4(13.33%)	0.353
Headache, n(%)		3(10.34%)	8(26.67%)	0.181
Vomit, n(%)		4(13.33%)	2(6.67%)	0.671
Chest pain, n(%)		2(6.90%)	5(16.67%)	0.424
Hemoptysis, n(%)		0(0%)	3(10.00%)	0.237
WBC count (× 10^3/μl), mean (SD)		6.60(3.65)	6.43(3.69)	0.861
Lymphocyte (count/μl), mean (SD)		1082.68(582.17)	1042.52(590.81)	0.792
HB (g/dl), mean (SD)		13.35(2.29)	12.65(2.06)	0.218
PLT (× 10^3/μl), mean (SD)		194.20(83.75)	203.30(74.64)	0.658
AST (u/l), mean (SD)		35.93(15.92)	33.93(13.96)	0.607
ALT (u/l), mean (SD)		31.73(8.57)	34.43(9.69)	0.258
LDH (u/l), mean (SD)		619.20(212.10)	599.67(197.93)	0.714
CRP (mg/dl), mean (SD)		41.30(28.86)	58.13(52.80)	0.132
ESR (mm/hour), mean (SD)		60.00(30.71)	66.03(30.45)	0.448
Body temperature upon admission(°C), mean (SD)		37.03(0.80)	37.93(0.92)	< 0.001
3rd day temperature(°C), mean (SD)		36.73(0.36)	37.24(0.69)	0.001
Body temperature at discharge(°C), mean (SD)		36.76(0.47)	36.85(0.46)	0.454
SPO2 upon admission(%), median (IQR)		86.0(82.0–88.0)	87.5(85.0–88.0)	0.148
3rd Day SPO2(%), median (IQR)		90.5(88.0–92.0)	88.0(80.0–91.0)	0.014
SPO2 at discharge(%),median (IQR)		93.5(91.0–95.0)	92.5(92.0–94.0)	0.406
ICU length of stay(day), median (IQR)		5.50(5.0–10.0)	5.0(5.0–7.0)	0.381
Hospital length of stay(day), median (IQR)		8.50(7.0–12.0)	6.50(4.0–12.0)	0.028
Expire, n(%)		3(10.00%)	3(10.00%)	> 0.9
Intubation, n(%)		5(16.67%)	4(13.33%)	> 0.9

SD: Standard deviation, n: count, IQR: interquartile range (25%-75%), COPD: Chronic obstructive pulmonary disease, WBC: White blood cell, HB: Hemoglobin, PLT: Platelet, AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SPO2: Oxygen saturation, ICU: Intensive care unite

Outcomes

There was no significant difference in body temperature at the time of discharge between the two groups (p value > 0.05)(Table 1). The mean body temperatures upon admission and on the 3rd day of admission were significantly higher in the control group (p value = 0.001). The mixed-design analysis of variance model (ANOVA) performed to evaluate the effect of time on body temperature at the time of admission, on the 3rd day of admission and discharge, showed a significant effect of time on body temperature (Wilks' Lambda = 0.589, F (2,57) = 19.879, p value < 0.001)(Fig. 2). Post hoc comparison indicated a significant difference between body temperatures at time of admission, discharge, and on the 3rd day of hospitalization (p value < 0.001).

SpO2 at admission and discharge were not significantly different between the two groups (p value > 0.05) (Table 1). SpO2 on the 3rd day of admission was higher in the case group compared to the control group (median, 90.5% *vs.* 88.0% respectively, p value = 0.014) (Table 1). A non-parametric Friedman test of difference among repeated measures of SpO2 was conducted and there was a significant difference in mean ranks in both groups with the oxygen saturation increasing significantly in both groups (p value < 0.001). The case group had a median length of admission in the hospital of 8.5 (range: 7.0–12.0) days which was significantly longer than the control group with a median length of admission of 6.5 (range: 4.0–12.0) days. There was no significant difference in the length of ICU stay between the two groups (p value > 0.05, Table 1). There was a non-significant higher rate of intubation in the case group (p value > 0.05) (Table 1). Death rate was equal in both groups (three deaths in each group, p value > 0.05). During treatment with high-dose vitamin C, none of the patients experienced adverse events such as headache, nausea, bloating, or abdominal discomfort.

Table 2
Identifier and details of studies which investigated the advantages of high dose vitamin C in patients with COVID-19

Identifier	Study type	Estimated Enrollment	Allocation	Masking	Arms	Primary Outcome Measures	Estimated Study Completion Date
NCT04342728*	CT	520	R	O/L	**Arm 1**: 8000 mg of ascorbic acid (daily with food) **Arm 2**: 50 mg of zinc gluconate (daily) **Arm 3**: 8000 mg of ascorbic acid and 50 mg of Zinc gluconate	Symptom Reduction in 28 days	April 30, 2021
NCT04357782[1]	CT	20	N/R	O/L	**Arm 1**: 50 mg/kg L-ascorbic acid (every 6 h for 4 days) in the group with mild deoxygenation **Arm 2**: 50 mg/kg L-ascorbic acid(every 6 h for 4 days) in the group with sever deoxygenation	1.Incidence of adverse events 2. Incidence of serious adverse reactions 3. Incidence of adverse reactions	August 1, 2020
NCT04323514[1]	O	500	N/A	O/L	10 gr of vitamin C intravenously in addition to conventional therapy	In-hospital mortality	March 13, 2021
NCT04344184*	CT	200	R	Q	**Arm 1**: 100 mg/kg intravenous vitamin C infusion (every 8 hour 3 days) **Arm 2**: Dextrose 5% Water	ventilator-free days	May 2021
NCT04264533*	CT	140	R	T	**Arm 1**: 50 ml injection: 12 g Vitamin C + Water (every 12 hours for 7 days) **Arm 2**: 50 ml of sterile water (every 12 hours for 7 days)	Ventilation-free days	September 30, 2020
IRCT20190917044805N2**	CT	60	R	D	**Arm 1**: 200 ml volume including 12000 mg of vitamin C in dextrose 5% for 4 days **Arm 2**: 200 ml of Distilled water in dextrose 5%	1. Time to clinical improvement (TTIC) 2. Time to clinical improvement (TTIC) of NEWS2 (National Early Warning Score 2)	N/A

CT: Clinical Trial, O: Observational study, R: Randomized, N/A: not available, N/R: non-randomized, T: Triple blinded, Q: Quadruple blinded, D: Double blinded, O/L: Open label, *: ClinicalTrials.gov, **: irct.ir

Identifier	Study type	Estimated Enrollment	Allocation	Masking	Arms	Primary Outcome Measures	Estimated Study Completion Date
IRCT20200324046850N5**	CT	40	R	D	**Arm 1**: Main regime + 500 mg of vitamin C **Arm 2**: Main regime + Placebo of vitamin C	Number of hospital admission days	N/A (Recruitment completed)
IRCT20151228025732N52**	CT	30	R	O/L	**Arm 1**: 2000 mg of Vitamin C every 6 hour for 7 days + main regime **Arm 2**: Only the main regime	1.The rate of decline in lung infection rate 2. Number of breaths per minute 3. The course of the disease 4. Heart rate	N/A (Recruitment completed)

CT: Clinical Trial, O: Observational study, R: Randomized, N/A: not available, N/R: non-randomized, T: Triple blinded, Q: Quadruple blinded, D: Double blinded, O/L: Open label, *: ClinicalTrials.gov, **: irct.ir

Discussion

Until the time of this study, no definite treatment option has been suggested and cleared for COVID-19. While this pandemic is still responsible for death of almost a million people and infection of many more, search for better treatment options should never be delayed. [20, 21]. Vitamin C is an essential water soluble nutrient that has different important roles in our body, especially in immune cell functions [1, 2, 4]. Studies report that vitamin C can be effective in treatment of bacterial and viral infection. These studies showed vitamin C weakly inhibits the multiplication of viruses such as influenza type A, Herpes simplex virus type 1 (HSV-1) and poliovirus type 1 [22–24]. A clinical study showed the effect of IV vitamin C therapy on reduction of IgG and IgM antibody levels in EBV infection [11]. There is also a report of a case of enterovirus/rhinovirus induced ARDS where the infusion of high-dose intravenous vitamin C was associated with rapid resolution of lung injury [12].

Some studies showed that serum vitamin C levels may plummet in some patients especially in the critically ill during the course of infection [25, 26]; and vitamin C deficiency may contribute to organ injury and immune paralysis which leads us to assume high-doses of vitamin C might improve clinical outcomes of critically ill patients [25]. There is also some evidence that shows vitamin C may reduce patients' susceptibility to lower respiratory tract infections such as pneumonia and it may have a protective role in lung infections but, further studies need to evaluate the efficacy of treatment with vitamin C in severe viral respiratory tract infections [25–29].

A number of meta-analysis demonstrated that the use of intravenous vitamin C as a therapy for sepsis and ARDS has benefits such as a lower rate of vasopressor requirements, shorter duration of both mechanical ventilation and admission in the ICUs; along with a shorter hospital admission in critically ill patients [18, 30–32]. Lin et al., found that administration of more than 50 mg/kg daily vitamin C had a significant effect in reduction of mortality rate in patients with severe sepsis. They concluded that a better survival rate correlated with administration of high doses of vitamin C [33]. Fowler et al., reported in their randomized, double blind, placebo-controlled, multicenter trial that high doses of vitamin C did not significantly improve organ dysfunction scores in patients with severe sepsis or ARDS but in three secondary outcomes, use of vitamin C was associated with a significantly lower risk of mortality on the 28th day after diagnosis of the infection (29.8% *vs.* 46.3%), a higher number of ventilator-free days (13.1 *vs.* 10.6 days) and a higher number of ICU-free days (10.7 *vs.* 7.7 days) [34].

All these findings emphasize possible beneficial effects of vitamin C as a treatment for COVID-19. Here, we conducted a randomized clinical trial with 60 patients in two groups. Thirty patients were treated with 1.5 grams of IV vitamin C, every 6 hours for 5 days in addition to the main treatment regimen (case group), whereas the other 30 patients were treated only with the standard regimen. Demographic characteristics, underlying diseases, and clinical and laboratory findings were not significantly different between the two groups. Fever and myalgia were significantly more frequent in the control group but, other clinical findings were not notably different. SpO2 was improved in all patients. There is a similar report of SpO2 improvement in China associated with

treatment with high doses of intravenous vitamin C (doses range from 2 to 10 grams per day in 8-10-hour IV infusions) in 50 moderate to severe COVID-19 patients. They also reported that all patients were cured and discharged [35]. The absence of a control group weakened the conclusions based on this report.

In the present study, there was no significant difference in oxygen SpO2 levels between the two groups at discharge but the median of SpO2 levels were significantly higher in the case group on the 3rd day of admission. The mean body temperature significantly decreased during the admission in both groups and there was no significant difference between two groups regarding the core body temperature at discharge but, on the 3rd day of treatment, the mean of patients' body temperature was significantly lower in the case group. Length of stay in the hospital had a median of 8.5 days and it was unexpectedly higher in the case group (8.5 *vs.* 6.5, p value = 0.028). Other outcomes including number of deaths, number of intubations and duration of ICU admission were not significantly different between two groups. We did not find any side effects in the patients. Other studies also reported good tolerance of high-dose vitamin C in their trials [36].

There are not enough data and clinical trials that have evaluated the correlation between high- dose vitamin C treatment in COVID-19 patients with ARDS and improvement of their status but, there are several ongoing studies that aim to investigate the impact of high-dose vitamin C on COVID-19 patients (details of ongoing studies are presented in Table 2). Investigators in these studies will assess primary outcomes such as 50% reduction in symptoms score in 28 days, incidence of adverse effects (including severe adverse reactions), time to clinical improvement (TTIC), TTIC of NEWS2 (National Early Warning Score 2), number of hospital admission days, the rate of decline in lung infection rate, in-hospital mortality rates and number of ventilator-free days. Based on estimated dates, none of these studies will be completed before August 1st 2020. The findings of these studies will be valuable and we hope to see promising results in their studies.

Our study has its own limitations which can be covered in the future studies. The open label design of the study and relatively small patient population are the main limitations. Further randomized double-blind clinical trials with more patient population can be beneficial.

Conclusion

In this study, we found that there were improvements in peripheral oxygen saturation and body temperature in both groups during the time of admission but we did not find significantly better outcomes in the group who were treated with high-dose vitamin C in addition to the main treatment regimen at discharge.

Declarations

- **Ethics approval and consent to participate:** The project was approved by TUMS ethics board. (IR.TUMS.VCR.REC.1399.078) IRCT20200411047025N1
- **Consent for publication:** Not applicable
- **Availability of data and materials**: Not applicable
- **Competing interests:** The authors declare that they have no competing interests
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Figures

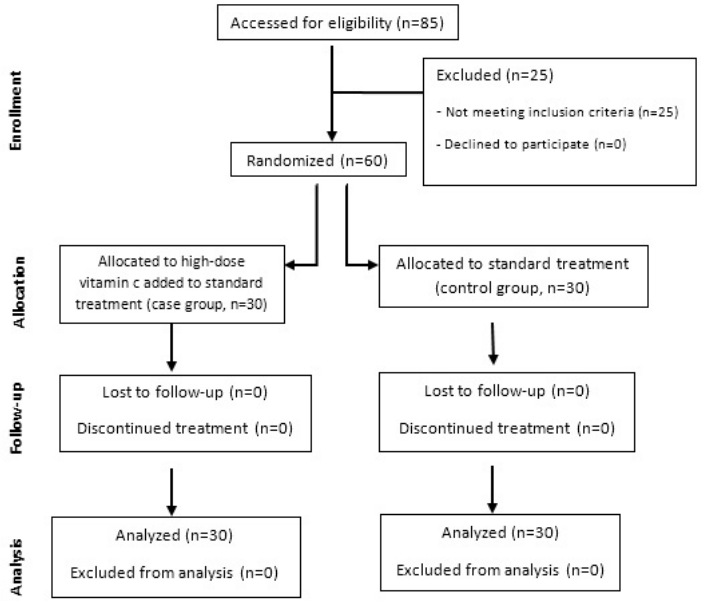

Figure 1

Randomization and treatment assignment.

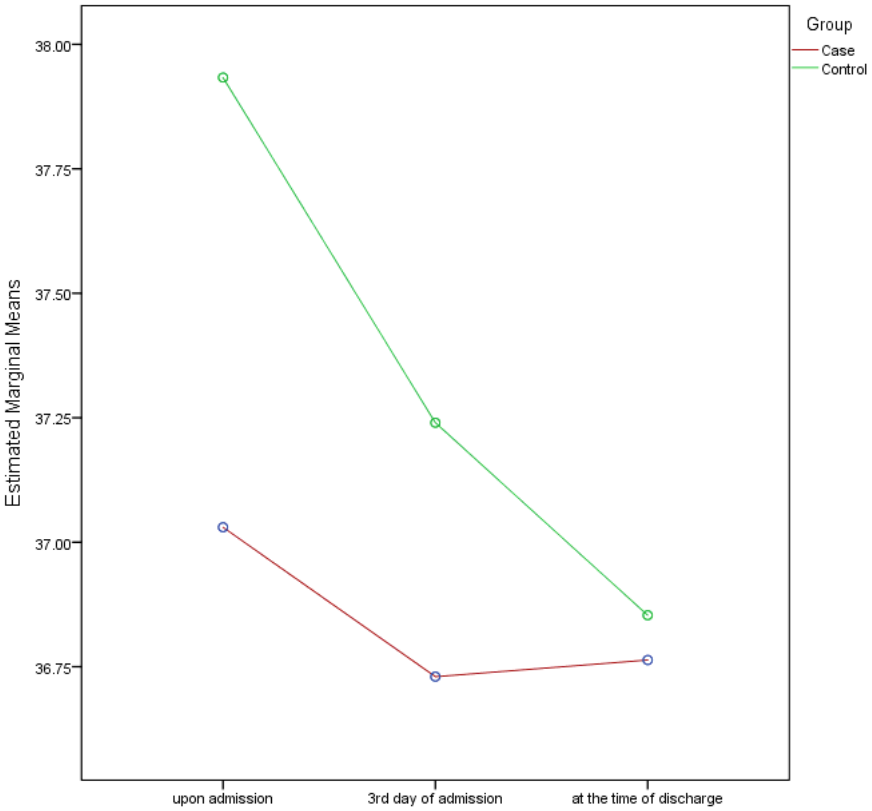

Figure 2

Body temperature means through time in the case and control group