Effect of Post-Treatment Fluvastatin for Hemorrhagic Shock in Rats

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Original research

Keywords: Hemorrhagic shock, traumatic shock, cytokine, HMG-CoA reductase inhibitor

Posted Date: May 7th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-25702/v1

Abstract

Background

To investigate the biochemical, histologic, and immunologic effects of post-treatment use of fluvastatin in cases of hemorrhagic shock in a rat model.

Methods

Experimental rats were randomly divided into four groups: (1) the control group received no drugs and did not undergo hemorrhagic shock (HS); (2) the control + statin group received fluvastatin 1 mg/kg without HS; (3) the HS group received normal saline after HS; (4) the HS + statin group received fluvastatin 1 mg/kg + normal saline after HS. HS was induced by femoral arterial catheter blood extraction of 30% of the total blood volume. Mean arterial pressure and heart rate were monitored for 2 h after starting blood withdrawal. Arterial blood gas, complete blood count, and serum cytokine levels were measured at baseline, 2 hrs after HS, and 48 hrs after resuscitation. Kidney, lung, and small intestines were removed for pathological examination 48 h after HS.

Results

The HS and HS + statins groups showed reduced bicarbonate, base excess, and platelet counts, all of which differed significantly from values in the control and control + statin groups at the end of the resuscitation period. The HS + statin group exhibited significantly elevated serum IL-10 2 hrs after resuscitation compared with the control group ($P < 0.05$). Except for IL-10, the group-time interaction was not significant for other cytokine profiles.

Conclusion

This study demonstrated that post-treatment with fluvastatin increased anti-inflammatory cytokines IL-10 production and affected cytokine profiles in rats after HS.

Background

Despite advances in trauma care, the leading cause of trauma death is exsanguination resulting in hemorrhagic shock (HS), which is seen in up to 30% of cases.(1) HS may result in multiple organ dysfunction and eventual death due to reduced tissue perfusion and subsequent cellular hypoxia, which occurs through several inflammatory pathways including leukocyte activation and organ sequestration. The current view holds that a dysfunctional systemic inflammatory response syndrome is central to the pathogenesis of multiple organ failure (MOF). Proinflammatory cytokine release after shock is central to the inflammatory response and has been described in animal models of hemorrhagic and traumatic

shock. Overwhelming production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) can lead to hemodynamic instability. If this process is not controlled by anti-inflammatory cytokines such as interleukin-10 (IL-10), it can lead to multiple organ dysfunction and death after HS.(2)

HMG-CoA reductase inhibitors (statins) exhibit important immunomodulatory effects independent of any lipid-lowering effect that they may elicit.(3) A novel lipid-independent mechanism of action for statins that is unrelated to their inhibitory potential on HMG-CoA reductase has recently been defined. Some previous studies showed that statins may exert an anti-inflammatory effect by binding to a specific site of lymphocyte function associated antigen-1 (LFA-1) on leukocytes and found that pre-treatment with fluvastatin suppressed the release of tumor necrosis factor-α (TNF-α), increased interleukin-10 (IL-10) production, and decreased levels of organ injury markers in endotoxic shock in rats.(4, 5) Furthermore, a post-treatment test giving fluvastatin to mice appeared to prolong survival following cecal ligation and puncture (CLP)-induced sepsis.(6) Since HS can produce the same inflammatory effects as endotoxic shock after LPS, it is possible that fluvastatin may also play a protective role in HS. Recent experimental studies showed that pre-treatment with fluvastatin suppressed the release of TNF-α, increased IL-10 production, and decreased markers of organ injury after induction of HS in rats.

To the best of our knowledge, no previous studies have focused on the effects of post-treatment with fluvastatin upon HS and the expression levels of multiple cytokines including IL-6, IL-10, IL-1β, IL-12p70, TNF-α, and IFN- γ. The aim of our study was to investigate the biochemical, histologic, and immunologic effects of post-treatment use of fluvastatin in cases of HS in a rat model.

Methods

Subjects

Forty male Sprague-Dawley rats (weight, 295.7 ± 22.3; age, 8–9 weeks old; Charles-River, Montreal, Quebec, Canada) were used and housed at the university animal center in a controlled environment at 22 ± 2 °C with a 12-hour light/dark cycle. The rats had unlimited access to food and water before the experiment.

Methods

Animal preparation

Animals were anesthetized with an intramuscular injection of 1 cc/kg tiletamine/zolazepam (Zoletil®, Virbac, France). After sterile left-groin dissection, a 24-gauge catheter was cannulated into the femoral artery to monitor blood pressure, sample blood, and withdraw blood. Another 24-gauge catheter was inserted into the femoral vein for fluid infusion and intravenous drug administration. The surgical procedure was completed in 15 minutes, and the incision was less than 0.5 cm^2 in length, as small as possible. Heparin (80 IU/kg) was administered to prevent clotting in catheters. The femoral artery catheter was connected to a blood pressure transducer (FE221, AD Instruments, NSW, Australia), and systolic and

diastolic blood pressure, mean arterial pressure (MAP), and heart rate were continuously recorded using PowerLab® (AD Instruments, NSW, Australia).

Experimental design

Animals were randomly divided into four groups. Group 1 was the control group, did not receive any drugs, and was not subjected to HS. Group 2 was the control + statin group, and these animals received 1 mg/kg fluvastatin (Novartis Pharmaceuticals, Cambridge, MA, USA) without HS induction. Group 3 was subjected to HS and received normal saline after HS. Group 4 was the HS + statin group, and these subjects received 1 mg/kg fluvastatin + normal saline after HS induction. Fluvastatins were given immediately after the first blood sampling in group 2 or after 30 min of bleeding in group 4. The doses of drug given to rats were the same as a previous study.(7) Animals were randomized into equal-sized groups using a free online calculator offering random sample allocation. The mean weights of groups were: control, 293.7 ± 21.79 g; control + statin, 298.4 ± 14.97 g; HS, 298.8 ± 25.97 g; HS + statin, 291.0 ± 26.66 g. There were no statistically significant differences in body weight between the 4 groups. Blood was withdrawn through the femoral artery until MAP decreased to 60 mmHg. Rats were infused with normal saline to 3 times the volume of blood loss for fluid resuscitation. The animals were moved to a cage after resuscitation. Rats were allowed free access to food and water after experiment completion. Acetaminophen (Children's Tylenol suspension1, Janssen, Seoul, Republic of Korea) was mixed with water to control pain in rats. The total duration of this study was 48 hours and observation of rat health and behavior was performed every 12 h for 48 h to assess survival. Rats that survived to 48 h were euthanized by decapitation under terminal anesthesia. The endpoint of our study included the survival of the rats until 48 hrs, so euthanasia was performed on live rats after that. Gross necropsy was performed on all rats, and all experimental processes are summarized in Fig. 1.

Blood sampling and measurements

Arterial blood gas such as pH, PO2, PCO2, HCO3, and excess base were measured at baseline, 2 hrs after HS, and 48 hrs after resuscitation. Complete blood count (CBC) including leukocyte count, hemoglobin, hematocrit, and platelet count were also measured at baseline, 2 hrs after administration of shock, and 48 hrs after resuscitation. Arterial blood gas testing was conducted using a point-of-care laboratory instrument (iSTAT, Abbott, Abbott Park, IL, USA) and test cartridges (CG3; Abbott). CBC testing was conducted using a CBC measuring instrument (Hemavet 950FS, Drew Scientific, USA). Serum cytokines including interleukin (IL)-1β, IL-6, IL-10, IL-12p70, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α were measured at baseline, 2 hrs after administration of shock, and 48 hrs after resuscitation. IL-1β, IL-6, IL-10, IL-12p70, IFN-γ, and TNF-α concentrations in blood samples were measured using a Multiplex kit (Bio-Rad, San Diego, USA) and run on Luminex technology (Bio-Plex Multiplex Bead Array System, Bio-Rad Hercules, CA, USA) according to the manufacturer's instructions.

Histological examination

Lung, duodenum, and kidney specimens were removed immediately after sacrifice, fixed overnight in 4% buffered formaldehyde, processed by standard methods, and stained with hematoxylin and eosin. A pathologist blinded to group enrollment subjected the lungs, duodenums, and kidneys to histopathological examination. All evaluations were made on five fields per section and five sections of lung, duodenum, and kidney.

Statistical analysis

Data are presented as mean ± standard error of the means (S.E.M.), mean ± standard deviation (S.D.) or median ± range, unless otherwise stated. Using repeated-measures ANOVA and Fisher's protected *t*-test, the significance of differences in measured values among groups was analyzed. SPSS 20.0 (SPSS, Inc., Chicago, IL, USA) was used to analyze the data. P-values less than 0.05 were considered statistically significant.

Results

Arterial blood gas and complete blood count

No significant differences in laboratory values were found at baseline among the four groups (Tables 1). The HS group and HS + statin group had low bicarbonate, base excess, and platelet count, all of which differed significantly from values in the control and control + statin groups at the end of the resuscitation period. Baseline hemoglobin and hematocrit did not vary among the four groups, but they decreased significantly after blood loss at 2 hrs in the HS and HS + statin groups. Base excess and bicarbonate had recovered by 48 hrs after resuscitation in all groups, but the hemoglobin and hematocrit of the HS group and HS + statin group remained lower than those of the control group and control + statin group.

Plasma interleukin (IL)-1β, IL-6, IL-10, IL-12p70, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α

Serial measurements of plasma interleukin (IL)-1β, IL-6, IL-10, IL-12p70, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α levels versus time plots are shown in Fig. 2. On repeated-measures ANOVA, the HS + statin group showed significantly elevated levels of serum IL-10 2 hrs after resuscitation compared with the other groups (*$P < 0.05$;). The HS group showed significantly elevated levels of serum TNF-α 2 hrs after resuscitation compared with the control group and control + statin group (*$P < 0.05$). The HS group and HS + statin group showed significantly elevated levels of serum TNF-α 24 hrs after resuscitation compared with the control group (*$P < 0.05$). Regarding other cytokine profiles, the group-time interaction was not significant among the four groups during the observation period.

Mean arterial pressure (MAP) and heart rate (HR)

Initial MAP was higher than 140 mmHg in all groups. MAP decreased rapidly after controlled bleeding in the HS group and HS + statin group ($P < 0.05$; Fig. 3). After 2 hrs, the MAP of the HS group and HS + statin

group stayed relatively was not different compared to the control group and control + statin group. HR significantly decreased after bleeding in the HS group and HS + statin group ($P < 0.05$; Fig. 3).

Total amount of fluid resuscitation

Normal saline was infused during the resuscitation period in all HS groups. Three blood samplings were conducted for each animal, and 1 cc of blood was withdrawn for each laboratory test. And then, the same volume of normal saline was infused for animals in all groups. The mean amount of total infused normal saline was 11.8 ± 3.3 mL in the control group, 13.1 ± 1.7 mL in the control + statin group, 53.2 ± 6.1 mL in the HS group, and 50.9 ± 5.2 ml in the HS + statin group. There were no differences in the volume of normal saline between the HS group and HS + statin group.

Survival rate

All rats in the control group, control + statin group, and HS + statin group survived for 48 hrs, whereas one of 10 rats in the HS group did not recover from HS during the observation period and died. There was no difference in mortality between all group. The other rats were all euthanized 48 hours after study initiation.

Histopathology of kidney, lung, and small intestine

There were no obvious histopathologic changes related to shock injury in the kidney, lung, and small intestine except for 1 case in the HS group. The most prominent histopathologic changes were observed in the lung tissue, including pulmonary hemorrhage and congestion. Neutrophils were also observed in lung tissue from the HS group (data not shown).

Discussion

This is the first study to investigate the effects of fluvastatin on the serum cytokine profile of rats when administered immediately after HS. Our study found that the serum cytokines of the HS group and HS + statin group exhibited different profiles of cytokine activation compared with those of the control and control + statin groups. Especially, the HS + statin group exhibited an increased serum IL-10 level 2 hrs after resuscitation compared with the control group, while the HS group did not.

Cytokines have a variety of functions. Pro-inflammatory cytokine activation after shock is very important to the inflammatory response and has been well described in animal experiments of hemorrhagic shock.(8–11) The pro-inflammatory role of TNF-α in the MOF condition has been established.(12, 13) A major function of TNF-α at the cellular level is to up-regulate production of IL-1β by macrophages. TNF-α stimulates endothelial proliferation, neutrophil adhesion, free radical formation, and IL-6 production. The role of IL-6 in the inflammatory reaction remains unclear, though previous studies have supported both pro-inflammatory and anti-inflammatory roles for this cytokine. IL-10, which has the ability to suppress cytokines and inhibit effector functions of immune cells, has been suggested to play an important role in counter regulation of the early inflammatory response.(14, 15) The proportion of IL-6 to IL-10 correlated well with the severity of injury in trauma patients in one clinical study.(16) During hemorrhage,

inflammatory cytokines such as TNF-α and IL-10 play important and early roles in HS-induced organ damage.(17, 18) Accordingly, there are several studies that attempt to suppress TNF-α, which is an important component of inflammation. Abraham, Jesmok (19) and Bahrami, Yao (20) found that hemorrhage and resuscitation-induced acute lung injury can be reduced through TNF-α monoclonal antibody therapy. In another study, administration of IL-10 depressed serum TNF-α production after HS in a rat model.

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are potent cholesterol-lowering drugs.(21) Many clinical studies have explored the effects of statins on the primary prevention of coronary heart disease and atherosclerosis.(22–24) In addition to its cholesterol-lowering properties, it can also exhibit pleiotropic effects such as endothelial function improvement, antioxidant properties, stabilization of atherosclerotic plaques, modulation of progenitor cells, suppression of inflammatory responses, and enhancement of certain immunomodulatory cytokine actions.(21, 25, 26)

A study by Lee, Lee (7) found that pretreatment with fluvastatin resulted in a decrease in HS-induced serum TNF-α level and an increased IL-10 production. These results suggest that fluvastatin reduced the production of pro-inflammatory cytokines and increases the production of anti-inflammatory cytokines, thereby preventing HS-associated multi-organ damage. Our study showed that serum TNF-α level tended to decrease in the HS + statin group compared to the HS group. However, pro-inflammatory cytokines were not significantly decreased in the HS + statin group. On the other hand, a study by Chen, Lee (5) revealed that fluvastatin can increase plasma IL-10 production when given after the onset of sepsis in a rat model and may have therapeutic effects in treatment of LPS-induced shock. These results are consistent with our findings. In this study, treatment with fluvastatin after HS resulted in higher IL-10 production than in the HS-only group 2 hrs after HS. This result suggested that post-treatment with fluvastatin elevates serum anti-inflammatory cytokines. However, these immunomodulatory effects were somewhat weak compared to pre-treatment with fluvastatin. In addition, cytokine profile differences had little effect on laboratory and other measured parameters in the HS + statin group. This may be associated with the therapeutic dosage or pharmacokinetics of fluvastatin used in our study. A previous study on the effects of intravenous rosuvastatin for acute stroke showed that it provided protection at concentrations of 0.2 and 2.0 mg/kg, but not at 0.02 mg/kg,(27) which could have been a similar factor in our experiments. Moreover, because the elimination half-life averages 0.7 hours for intravenous fluvastatin, multiple doses may be needed.(28) Further studies are required to investigate the optimal treatment dosage of fluvastatin for post-treatment use in HS.

Our study had some limitations. First, we used a rat model of controlled HS, which does not completely reflect the clinical situation. However, because we wanted to compare the cytokine levels of four groups over time and needed to ensure similar blood loss between groups, a controlled model of HS was most appropriate. Moreover, the discrepancies in shock severity in an uncontrolled HS model could have acted as significant confounding factors. Second, the experiment was conducted with only 30% blood loss (moderate HS). Therefore, this amount of bleeding may have been insufficient to cause changes in the

various cytokines that affect immune status in a rat HS model. Greater blood loss would likely lead to greater differences in the outcomes of fluvastatin treatment for HS.

Conclusion

This study showed that post-treatment with fluvastatin did not significantly suppress pro-inflammatory cytokines but did elicit a meaningful increase in anti-inflammatory cytokine IL-10 production. In this rat model, cytokine profiles after HS were altered by fluvastatin treatment.

Abbreviations

CBC
Complete blood count
CLP
cecal ligation and puncture
HMG-CoA
Hydroxymethylglutaryl coenzyme A
HR
heart rate
HS
hemorrhagic shock
IACUC
Institutional Animal Care and Use Committee
IFN
interferon
IL-10
interleukin-10
LFA-1
lymphocyte function associated antigen-1
MAP
mean arterial pressure
MOF
multiple organ failure
S.D.
standard deviation
S.E.M.
standard error of the means
TNF-α
tumor necrosis factor-α

Declarations

Ethics approval and consent to participate

The Animal Use and Care Protocol for this animal experiment was approved by the Institutional Animal Care and Use Committee (IACUC) at Wonju Campus, Yonsei University, Gangwon, Wonju, Republic of Korea (no. YWC-130514-1). The researcher was trained in the basic procedural practices and processes related to the animal experiment.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

Original draft preparation: Oh Hyun Kim

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Acknowledgements

Not applicable

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Tables

Table 1. Laboratory values at Baseline and 2 and 48 hr after the Resuscitation Period

	Control Group (n=5)	Control + Statin Group (n=7)	HS Group (n=9)	HS + Statin Group (n=8)	P
Arterial Blood Gas Variables					
Baseline					
pH	7.32±0.44	7.33±0.05	7.32±0.03	7.32±0.43	0.778
PO_2 (mmHg)	97.8±8.2	86.6±7.4	88.5±7.2	87.6±10.6	0.162
PCO_2 (mmHg)	47.8±4.3	47.0±4.4	46.1±2.9	46.6±5.8	0.973
Base excess (mmol/L)	-1.4±1.1	-3.1±2.0	-2.3±2.1	-3.9±2.5	0.702
HCO_3^- (mmol/L)	24.6±1.0	24.8±1.3	23.9±1.6	24.0±2.2	0.604
2 hr after resuscitation					
pH	7.33±0.14	7.33±0.04	7.25±0.09	7.29±0.06	0.051
PO2 (mmHg)	79.8±11.5	86.9±10.6	93.0±23.5	90.8±14.0	0.394
PCO2 (mmHg)	39.9±4.7	43.5±3.3	43.0±6.7	36.7±8.3	0.142
Base excess (mmol/L)	-3.8±1.6	-3.1±2.0	-9.1±4.3*	-7.3±7.2*	<0.001
HCO3- (mmol/L)	21.7±1.7	22.7±1.5	16.7±5.7*	17.8±4.5*	<0.001
48 hr after resuscitation					
pH	7.39±0.02	7.40±0.02	7.41±0.04	7.39±0.03	0.576
PO2 (mmHg)	98.7±28.3.	80.0±6.2	75.4±16.4	87.0±13.2	0.428
PCO2 (mmHg)	43.1±2.5	42.5±3.4	41.9±5.5	29.3±5.0	0.521
Base excess (mmol/L)	1.0±1.7	1.3±1.3	2.0±2.7	-0.1±3.5	0.588
HCO3- (mmol/L)	26.1±1.8	26.2±1.4	26.6±2.6	24.1±3.7	0.553
Complete Blood Analysis					
Baseline					
WBC (x109/L)	6.45±2.99	5.67±2.85	5.92±1.80	6.27±3.58	0.956
Neutrophil count (%)	9.6±3.7	12.5±7.8	15.7±8.2	11.8±4.6	0.242
Lymphocyte count (%)	85.0±4.1	83.1±5.7	78.4±7.3	83.1±3.7	0.262
Hemoglobin (g/dL)	13.7±1.3	13.7±2.1	13.6±2.1	13.8±1.9	0.971
Hct (%)	44.6±8.8	42.4±7.2	43.8±7.0	43.6±6.7	0.909
Platelet count (x109/L)	694±81	664±78	699±73	693±75	0.761
2 hr after resuscitation					
WBC (x109/L)	8.9±5.6	9.6±5.2	8.2±5.0	10.1±4.3	0.811
Neutrophil count (%)	29.7±16.6	34.1±27.4	18.8±20.9	20.3±14.9	0.316
Lymphocyte count (%)	51.3±18.0	55.4±22.8	70.3±20.0	62.8±16.0	0.197
Hemoglobin (g/dL)	12.2±1.5	12.4±1.5	8.2±1.9‡	8.0±1.6‡	<0.001
Hct (%)	40.2±9.6	39.8±6.2	27.6±5.3‡	25.7±3.0‡	<0.001
Platelet count (x109/L)	653±73	646±80	564±57	526±84	0.021
48 hr after resuscitation					
WBC (x109/L)	5.5±4.0	6.6±1.5	4.8±1.7	6.7±2.1	0.241
Neutrophil count (%)	14.9±9.0	23.0±9.2	17.9±8.7	15.3±7.7	0.314

Lymphocyte count (%)	75.6±10.6	69.5±7.9	69.1±11.5	74.1±7.1	0.383
Hemoglobin (g/dL)	10.1±1.1	11.5±1.4	6.4±2.2‡	8.2±1.6‡	<0.001
Hct (%)	30.1±7.2	35.7±6.8	20.4±4.9‡	25.7±3.5‡	<0.001
Platelet count (x109/L)	700±350	602±102	556±145	698±81	0.241

Data are presented as mean and S.D.
Control group: did not receive drugs or undergo hemorrhagic shock (HS) procedures, control + statin group: received fluvastatin 1 mg/kg without HS, HS group: received normal saline after HS, HS + statin group: received fluvastatin 1 mg/kg + normal saline after HS.
*$P < 0.005$ when compared with the control group and control + statin group
‡$P < 0.001$ when compared with the control group and control + statin group

Figures

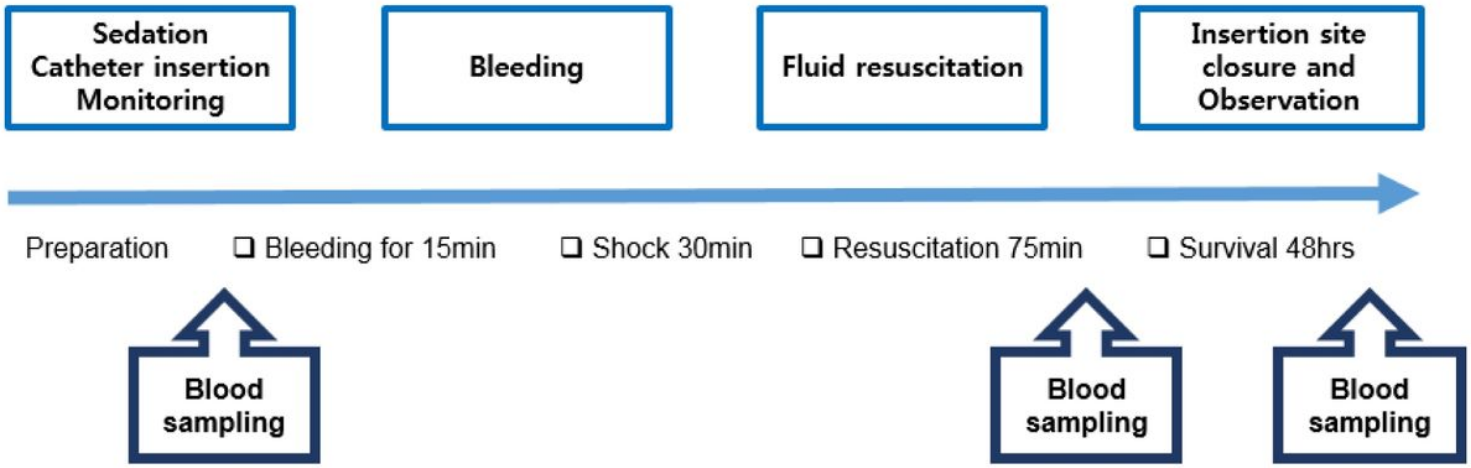

Figure 1

Experimental protocol in hemorrhagic shock in rats

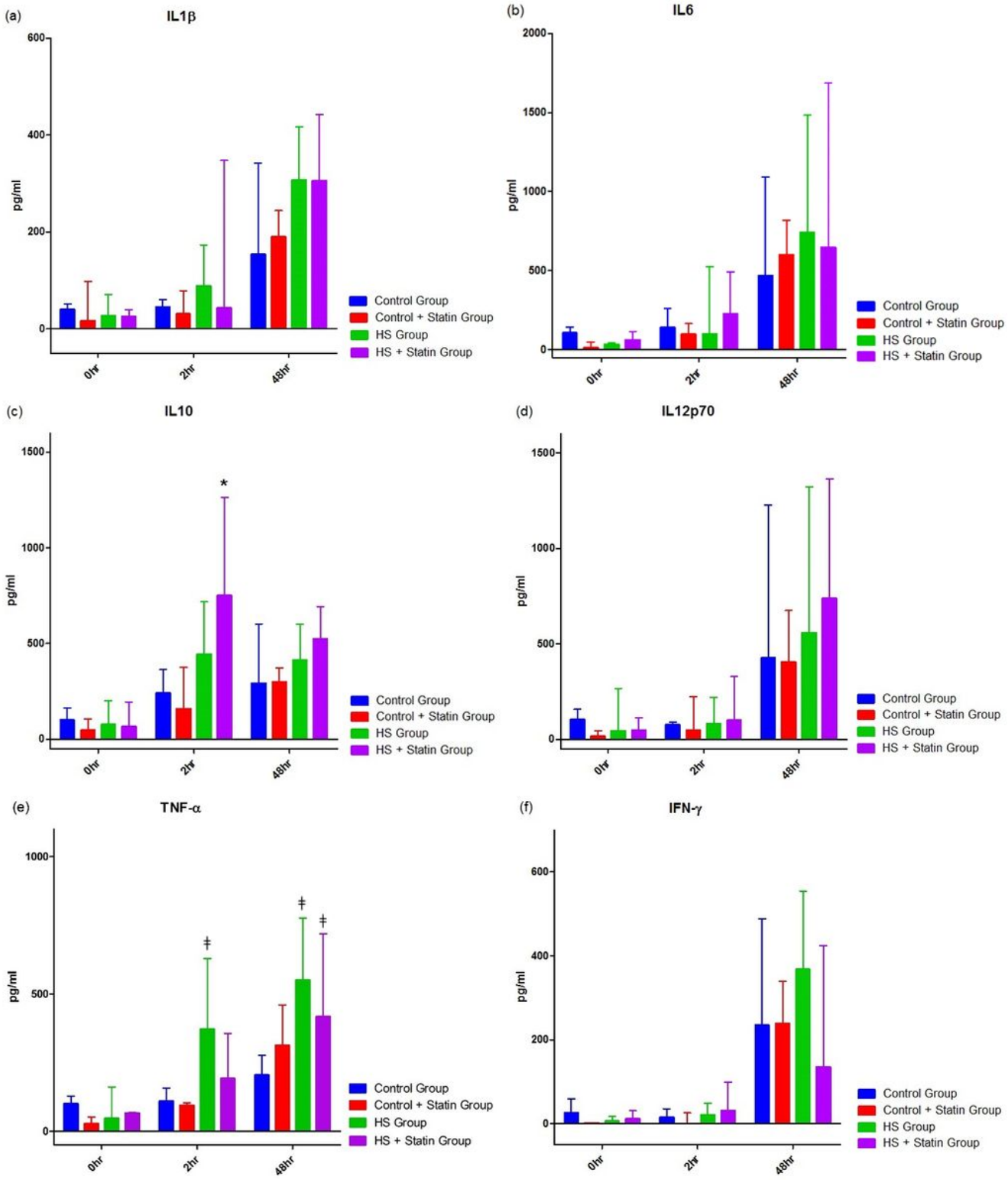

Figure 2

Changes in plasma interleukin (IL)-1β (a), IL-6 (b), IL-10 (c), IL-12p70 (d), tumor necrosis factor (TNF)-α (e), and interferon (IFN)-γ (f) in a hemorrhagic shock model. Data are presented as median and interquartile range. * Significant difference ($P < 0.05$): HS + Statin Group versus Control group, Control + Statin group and HS group ‡ Significant difference ($P < 0.05$): HS Group versus Control group and Control + Statin group; HS group versus Control group; HS + Statin group versus control group

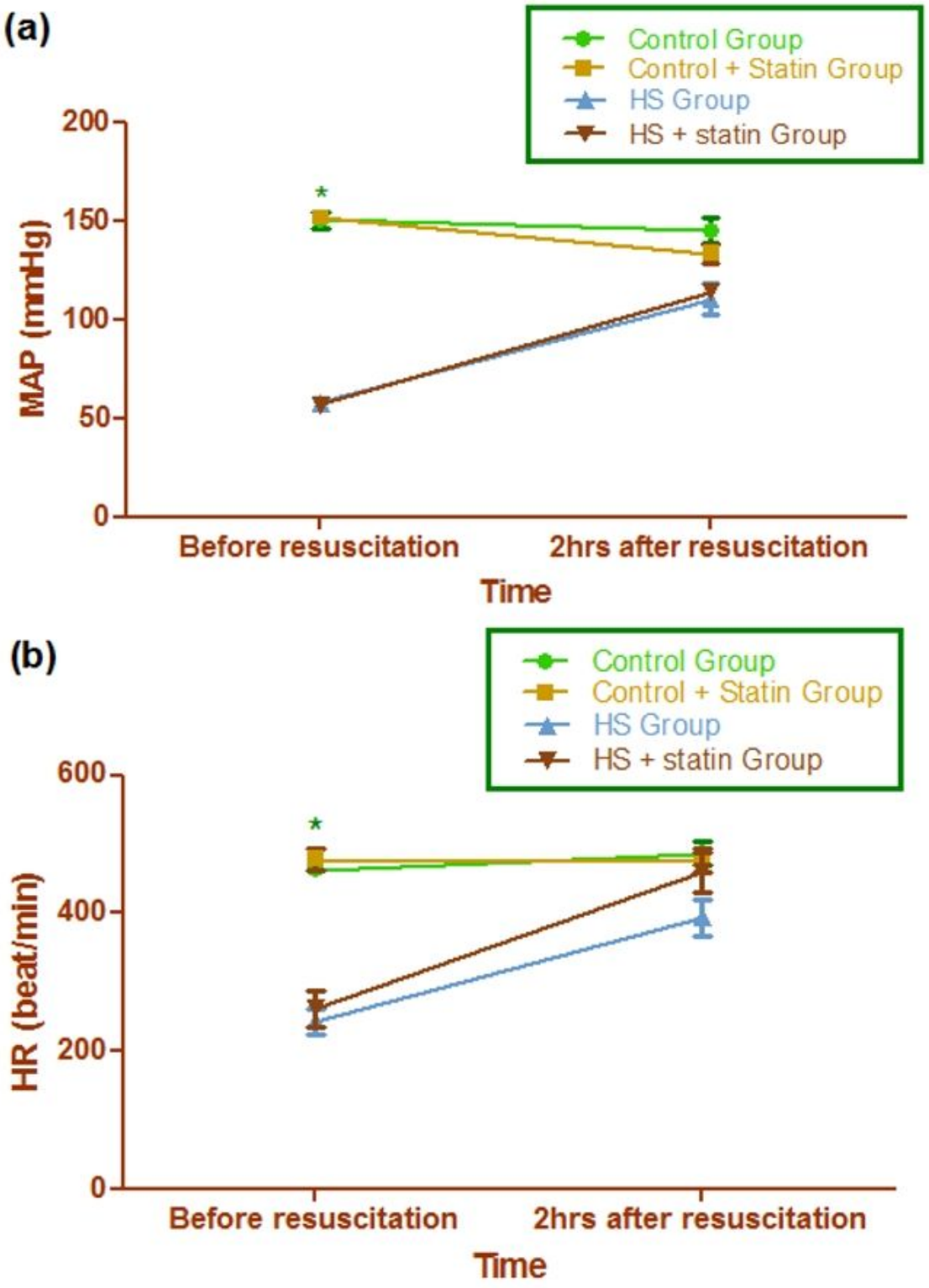

Figure 3

Change in mean arterial pressure (MAP) (a) and heart rate (HR) (b) in a hemorrhagic shock model. Data are presented as mean and S.E. * $P < 0.05$ for the HS group and HS + statin group compared with the control group and control + statin group. Control group: did not receive drugs or undergo hemorrhagic shock (HS) procedures, control + statin group: received fluvastatin 1 mg/kg and no HS, HS group: received normal saline after HS, HS + statin group: received fluvastatin 1 mg/kg + normal saline after HS.