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The Effect of Mindfulness Meditation Training on Biological Acute Stress Responses in Generalized Anxiety Disorder

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Abstract

Mindfulness-Based interventions have increased in popularity in psychiatry, but the impact of these treatments on disorder-relevant biomarkers would greatly enhance efficacy and mechanistic evidence. If Generalized Anxiety Disorder (GAD) is successfully treated, relevant biomarkers should change, supporting the impact of treatment and suggesting improved resilience to stress. Seventy adults with GAD were randomized to receive either Mindfulness-Based Stress Reduction (MBSR) or an attention control class; before and after, they underwent the Trier Social Stress Test (TSST). Area-Under-the-Curve (AUC) concentrations were calculated for adrenocorticotropic hormone (ACTH) and pro-inflammatory cytokines. MBSR participants had a significantly greater reduction in ACTH AUC compared to control participants. Similarly, the MBSR group had a

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All authors participated in the drafting the article or with revising it critically for important intellectual content and all authors gave final approval of the version to be published.

Declaration of Interest

Dr. Hoge reports grants from National Institutes of Health (K23AT4432) during the conduct of the study. Dr. Bui received funding from the National Institute of Health, the American Foundation for Suicide Prevention, the Highland Street Foundation, and from the U.S. Department of Defense during the conduct of the study. Ms. Palitz and Mr. Schwarz received funding from the National Institute of Health and the Highland Street Foundation during the conduct of the study. Ms. Owens received funding from Highland Street Foundation during the conduct of the study. Dr. Johnston has nothing to disclose. Dr. Simon received funding from the National Institute of Health, the American Foundation for Suicide Prevention, the Highland Street Foundation, and from the U.S. Department of Defense during the conduct of the study. Dr. Pollack reports grants from NIH during the conduct of the study; he was also an advisory board member or consultant for Eli Lilly, Medavante, Otsuka, and Transcept; Dr. Pollack also had equity in Medavante, Mensante Corporation, Mindsite, and Targa; he has received royalties from or holds patents on the SIGH-A and SAFER interviews.

greater reduction in inflammatory cytokines' AUC concentrations. We found larger reductions in stress markers for patients with GAD in the MBSR class compared to control; this provides the first combined hormonal and immunological evidence that MBSR may enhance resilience to stress.

Keywords

Meditation; Anxiety; Resilience; Stress Reactivity; Acute Stress; Mindfulness-Based Intervention; Psychological Stress

1. Introduction

Chronic or repeated psychological stress has been associated with abnormalities in stress hormones and inflammatory markers. These hormonal and immune abnormalities are in turn associated with negative health consequences such as cardiovascular disease risk and metabolic syndrome (Chrousos, 2000; Ridker et al., 2000). For example, chronic over-secretion of cortisol is associated with metabolic and hemodynamic disturbances such as high systolic blood pressure, fasting glucose, and insulin (Kaur, 2014). In addition, higher levels of circulating pro-inflammatory cytokines such as interleukin-6 (IL-6) are associated with other metabolic syndrome elements including higher body-mass index and the development of type 2 diabetes, and with an increased risk for coronary artery disease (Pradhan et al., 2002).

The causal link between hormonal and inflammatory markers and stress suggested by this body of cross-sectional data is supported by studies showing changes in these biomarkers in response to an experimental stress. Paralleling the epidemiological observations of chronically stressed populations, laboratory stress challenge tests have thus been found to provoke similar elevations in stress hormones (cortisol and adrenocorticotropic hormone (ACTH)) and markers of inflammation (tumor necrosis factor-alpha (TNF-alpha), and IL-6) in the bloodstream (Kirschbaum et al., 1993; Pace et al., 2006; von Kanel et al., 2005).

Mindfulness-Based interventions have greatly increased in popularity and have been used to treat anxiety in recent years. However, randomized and adequately controlled trials are needed to validate waitlist-controlled findings and provide additional confirmation of biological effects (Chiesa and Serretti, 2010; Goyal et al., 2014). Given that mindfulness meditation focuses on one's present experience is often ignored or avoided in Generalized Anxiety Disorder (GAD), we conducted a randomized, controlled study comparing Mindfulness-Based Stress Reduction (MBSR), a standardized and manualized mindfulness meditation training course, with an attention control, Stress Management Education (SME) in individuals with GAD. We measured the effect of MBSR *vs.* SME on clinical anxiety measures, and found a greater drop in anxiety ratings in most of our measures (see (Hoge et al., 2013) for detailed results). In a group of these patients, we examined resilience to subsequent stress by measuring hormones and inflammatory markers during the laboratory-based Trier Social Stress Test (TSST). Resilience is "the ability of individuals to adapt successfully in the face of acute stress, trauma, or chronic adversity, maintaining or rapidly regaining psychological well-being and physiological homeostasis" (Charney, 2004), and the

TSST, which provides a way to measure coping and recovery from a standardized stressor, has been used to assess resilience in the laboratory (Rose et al., 2013). Prior research has demonstrated that patients with GAD, like other chronically stressed populations, have an exaggerated stress hormone response to the TSST or other laboratory stress provocation, compared to healthy controls (Gerra et al., 2000).

Although participants' ratings of *subjective* stress were reduced more after MBSR compared to SME in our clinical study, we wanted to examine biomarkers in a separate planned analysis using blood markers previously linked to acute and chronic stress, such as the stress hormones cortisol and ACTH, and markers of inflammation, TNF-alpha and IL-6. We were interested in whether MBSR could improve coping and mitigate the physiological effects of acute stress. In addition, decreases in stress hormones and chronic inflammatory markers after mindfulness meditation, compared to a control intervention, would provide some support to the hypothesis that mindfulness meditation training may contribute to improvements in overall medical (cardiovascular and metabolic) health through reductions in stress related biological responses. We hypothesized that mindfulness meditation would mitigate the previously reported elevated response to acute stress observed in GAD, evidenced by a greater reduction in stress hormones and inflammatory markers with treatment.

2. Methods

2.1. Participants and Procedures

The procedures of the clinical randomized controlled trial have been described in detail previously (Hoge et al., 2013). Briefly, individuals age 18 and older with GAD, as determined by the Structured Clinical Interview for the DSM-IV (SCID) (First et al., 2002), were randomized to either a modified group MBSR or group SME (see below for course descriptions). Exclusion criteria included lifetime history of psychotic disorder, intellectual disability, organic medical disorders (such as endocrine diseases such as Addison's and Cushing's or chronic inflammatory diseases), bipolar disorder, post-traumatic stress disorder or obsessive compulsive disorder; current alcohol or substance abuse or dependence; significant suicidal ideation or behaviors; and concurrent psychotherapy for GAD. Additional inclusion criteria for this biomarker ancillary study were completion of the pre- and post-treatment TSST experiments, and the availability of blood specimens with adequate volume from all three TSST time periods: pre-stress, immediate post-stress, and later post-stress. In addition, we excluded patients taking antidepressants and benzodiazepines, as prior data suggest they may artificially alter the hormone response during the TSST (Bremner et al., 2003; Carpenter et al., 2007).

Prior to the start of the intervention class, and after baseline questionnaire measurements, participants came to the lab for a testing day, in which they completed the TSST and all blood testing (see details in section 2.2 below). After the end of the 8-week intervention, they returned to the lab for the second TSST. All study procedures were given ethical approved by the Massachusetts General Hospital/Partners Health Care institutional review board and all participants gave informed written consent before beginning the study.

Seventy-nine participants completed treatment in the parent RCT study (Hoge et al., 2013). Eligible for the biomarker analysis were the 72 participants (MBSR, n=43; SME, n=29) who agreed to blood collection. Some data were missing due to occasional processing or assay problems: intravenous catheter failure (n=1, MBSR), insufficient plasma quantity for multiple assays (n=5 in MBSR, n=4 in SME). Thus, because a minimum of three time points were required to calculate an Area Under the Curve (AUC), some participants' biomarkers AUC's could not be calculated. One participant was excluded from the biomarker analysis due to a post-randomization acute medical issue, and another due to lab error. Thus, the final sample size that contained both time points varied slightly for each stress marker: n=67 for ACTH, n=68 for cortisol, n=65 for TNF-alpha, and n=62 for IL-6.

2.2. The TSST

The TSST and blood collection procedures were conducted between 1:00pm and 4:30pm to control for hormonal diurnal variation. The TSST consists of an 8-minute public speaking task and a subsequent 5-minute mental arithmetic task (serial subtraction) performed in front of a panel of "evaluators" dressed in white lab coats and holding clipboards and a large, conspicuous video camera. The TSST procedure followed a detailed script to ensure its systematic and controlled delivery.

Because the TSST was administered before and at the end of the trial, several measures were taken to lower the potential for stress habituation and to improve methodological rigor for the second TSST: 1) the evaluators were switched so that they would be strangers the second time, 2) the TSST was moved to a different room, 3) a different arithmetic task was employed to avoid practice effects and 4) participants were told that their performance on the first speech was in the low range, and that this was their chance to improve their score [26].

2.3. Treatments

MBSR is an 8-week group-based intervention with a single weekend "retreat" day and daily home practice guided by audio recordings. In-class practices (breath-awareness, a body-scan, and gentle Hatha yoga) are used to cultivate awareness of internal present-moment experiences with an accepting, non-judgmental stance. The SME class was designed as an attention control intervention for MBSR to control for the non-specific effects of treatment, such as group support, attention from the instructor, and participants' expectations. The course is taught in a didactic format, and provides lectures on overall health and wellness such as diet, exercise, sleep, and time management. Importantly, SME does not contain any meditation or other mind-body intervention (Hoge et al., 2013).

2.4. Blood collection

An intravenous catheter was placed at time 0, and then the participant rested while pre-stress blood samples were collected (time +5, +10, +15, and +20 minutes). At +22 minutes, the speech task instructions were read to the participant. At the end of the 8-minute speech preparation time, blood was collected (time +28), and the participant was led to the testing room with the audience of evaluators. After the speech and arithmetic tasks, the subject was

led back to the phlebotomy room where post-stress blood samples were collected (+40, +45, +50, +55, and +80 minutes).

To assess effects of acute stress on the Hypothalamic-Pituitary-Adrenal (HPA) axis, we measured blood levels of cortisol and ACTH. To measure effects of acute stress inflammation, we assessed IL-6 and TNF-alpha.

2.5. Statistical Analyses

To be consistent with earlier published trials measuring hormone and cytokine response to the TSST, we compared the pattern of blood markers during stress pre- and post-treatment using an area under the curve (AUC) calculation (Pruessner et al., 1997; Wirtz et al., 2007). We calculated AUC with respect to increase for blood markers of stress for patients with cortisol, ACTH, TNF-alpha, and IL-6, with time point +5 as the baseline blood level, using all time points that were available (Pruessner et al., 2003). Then, we conducted a series of analyses of variance for repeated measures (repeated-measure ANOVA) with time (pre-treatment and post-treatment) as the repeated measure, treatment arm as between-subjects factor, and the AUCs as the dependent variables to examine the effect of group on the change in AUCs between baseline and endpoint. Statistical significance was set to alpha=0.05 (two-sided) for all analyses, and all analyses were conducted using Stata 12.1 (Stata Corporation, College Station, TX).

3. Results

Demographic characteristics by treatment group are presented in Table 1; there were no significant differences in gender, age, or race distribution. After randomization, 11 participants from the SME group dropped out, and 3 from the MBSR group dropped. Mean values and changes in AUC concentrations for hormone and cytokine levels between before and after the 8-week treatment, are shown in Table 2.

3.1. Endocrine Markers

The repeated-measure ANOVA with cortisol AUC as the dependent variable ($F(1,131)=4.50$, $p<0.0001$) found a main effect of time, ($F(1,63)= 11.04$, $p<0.001$) but no significant treatment arm X time interaction, ($F(1,63)=0.77$, $p=0.38$). However, there was a significant treatment arm X time interaction, $F(1,55)=7.75$, $p=0.007$ with the ACTH AUC's over the course of the treatment, with participants in the MBSR group exhibiting a reduction in their ACTH AUC, while those in the SME group increased (see Table 2).

3. 2. Immunological Markers

Comparison of the cytokine (IL-6 and TNF-alpha) AUC concentrations measured during the pre-treatment and post-treatment TSST's showed a decrease after treatment in the MBSR group, but an increase in the SME group (see Table 2). Calculations using a repeated-measure ANOVA with IL-6 AUC as the dependent variable ($F(1,134) =1.82$, $p<0.01$) found no main effect of time, $F(1,59)= 0.01$, $p=0.91$ but a significant treatment arm X time interaction, $F(1,59)=4.69$, $p=0.034$. Similarly, a repeated-measure ANOVA with TNF-alpha AUC ($F(1,136)=2.03$, $p<0.01$) found no main effect of time, $F(1,63)= 0.02$, $p=0.89$ but a

significant treatment arm X time interaction, $F(1,63)=4.57$, $p=0.036$. This difference further suggests that MBSR participants had a greater increase in stress resilience, as measured by response to the TSST stressor the second time (Table 2 and Figure 1).

4. Discussion

We found that mindfulness meditation training was associated with an attenuated stress response to laboratory stress in GAD, with evidence from both HPA axis hormones and inflammatory markers, raising the possibility that mindfulness meditation may imbue some resilience to stressful psychological challenges. The TSST is a well-validated, widely used laboratory-based model of psychological stress that can be used in a controlled fashion to understand the effects of potential real-world stressors (Kirschbaum et al., 1993). Therefore, the present findings help elucidate potential benefits of meditation training on psychological resilience in an at risk population with a preexisting anxiety disorder, GAD.

Our findings are consistent with other work demonstrating that meditation training may enhance biological resilience to laboratory stress. For example, Pace et al. demonstrated that healthy participants who did a high amount of compassion meditation practice had a faster drop in cortisol after the TSST than healthy participants who did a low amount of compassion meditation practice (Pace et al., 2010).

Interestingly, participants who did not practice meditation (those in the SME group) experienced *increased* stress in anticipation of the second TSST, rather than a habituation-related decreased level of stress, as has been suggested by studies of repeat TSSTs with healthy adults (Schommer et al., 2003). This observation is consistent with research with participants who were depressed, traumatized, or had ‘high exhaustion’; these groups had either a higher cortisol reactivity to the TSST compared to controls, or an increased sensitivity to the TSST when it was given a second time (Britton et al., 2012; Kudielka et al., 2006; Peckins et al., 2012). For example, when experiencing the TSST a second time, patients with a history of depression who did not receive treatment evidenced an increase in anticipatory (pre-stressor) anxiety (Britton et al., 2012), representing a model for increased risk for cumulative stress related effects in individuals with affective disorders.

The value of an intervention that can improve resilience to psychological stress in this vulnerable population cannot be overestimated. Multiple studies show that psychological stress can contribute to the onset, exacerbation, or relapse of anxiety disorders (Lteif and Mavissakalian, 1995; Watanabe et al., 2005). Although there are some limitations to using a lab stress to model life stressors, even improved laboratory stress coping has been directly linked to better mental health outcomes: Aschbacher et al. demonstrated that worse psychological coping during the TSST was associated with greater depression symptoms in the subsequent year (Aschbacher et al., 2012). Looking at the question clinically, studies involving patients with remitted depression found that mindfulness meditation training was associated with decreased risk for relapse to depression, suggesting that mindfulness meditation may improve coping and resilience (Segal et al., 2010; Teasdale et al., 2000).

Self-report of emotional states (such as anxiety, in this case) can be highly biased and unreliable, especially in GAD; some patients with GAD may have limited access to or difficulty describing internal processes (Salters-Pedneault et al., 2006). A recent review of TSST data found that only about 25% of studies found a correlation between stress hormone levels and self-reported emotional stress (Campbell and Ehlert, 2012). Biological measures of stress and anxiety used in this study are valuable since they overcome some of the limitations due to the inherent variability of self-report data associated with individual factors.

The observation of higher stress markers during the TSST in our and other's data may help explain the chronically high levels of circulating stress hormones and cytokines observed in individuals with anxiety disorders, who experience repeated stress due to their symptoms over months and years (Arranz et al., 2007; Mantella et al., 2008). This link between negative medical health outcomes and chronic elevations in inflammatory markers and stress hormones may help explain the higher rates of cardiovascular disease and metabolic syndrome in patients with anxiety disorders (Carroll et al., 2009; Roest et al., 2010). For example, the impairing, distressing, and often chronic generalized anxiety disorder (GAD) is associated with a greater risk of cardiovascular disease mortality (Tully et al., 2013). Thus, if this relationship is at all causal, successful treatment of anxiety disorders such as GAD may result not only in improved psychological health but also improved medical health, increasing the public health relevance of anxiety disorder treatment. Furthermore, some data suggest that normalization of stress and inflammation pathways may accompany successful treatment of chronic anxiety or conditions with chronic stress (Doering et al., 2007); however determination of mechanistic pathways may be difficult due to confounding effects of pharmacological treatments and medical illness on these systems.

There are some limitations of this study. First, conclusions are limited due to relatively small sample size, and exclusion criteria for study entry may limit the generalizability of our findings. Also, it is not clear why there were no significant differences in cortisol AUC changes between the groups, when the closely related ACTH changes were significantly different. One possibility is that due to the slower half-life of cortisol (compared to ACTH) and therefore longer persistence in the blood, cortisol may not be as reliable when measurements are taken close together (King et al., 2009). For example, in a study by Jezova et al., ACTH was found to rise with stress but not cortisol measurements taken at the exact same time (Jezova et al., 2013). Further, our hormonal mean plasma levels showed more variability than other published reports; however, the large majority of experiments using the TSST utilized healthy populations such as college students, and not a psychiatrically disordered population such as our GAD sample. Lastly, we did not include measures of potential confounds including religious belief, stressful life events, or socioeconomic status, however, since participants were randomized between MBSR vs. SME, we do not expect the two groups to significantly differ on these variables.

In conclusion, these findings suggest that mindfulness meditation training, a relatively inexpensive and low-stigma treatment approach, may be a helpful strategy to decrease biological stress reactivity and improve resilience to stressors in patients with GAD. Future

work should focus on the impact of mindfulness meditation on “real life” stress and anxiety disorder severity and relapse.

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Highlights

- Individuals with Generalized Anxiety Disorder who completed mindfulness meditation training had a greater drop in stress-related adrenocorticotropic hormone.
- Individuals with Generalized Anxiety Disorder who completed mindfulness meditation training also had a greater drop in proimflammatory cytokines.
- Findings suggest that mindfulness meditation training may have helped participants cope better with subsequent stress.

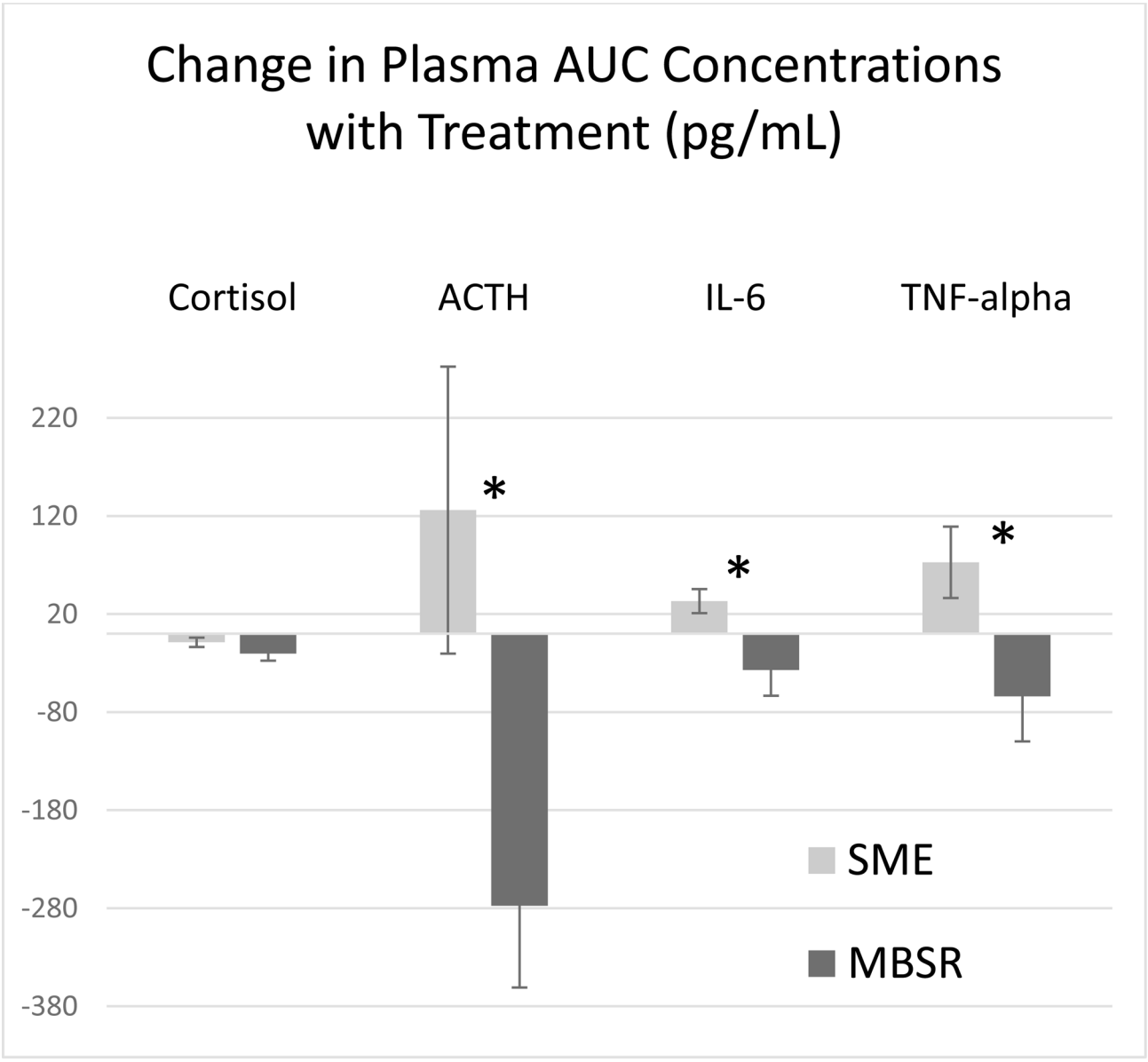

Figure 1.
Change in plasma area-under-the-curve (AUC) concentration with treatment (pg/mL)

Table 1

Demographic and Clinical Characteristics

Characteristic	MBSR (*n*=42)	SME (*n*=28)	*p*-value†
Gender: *n* (%)			0.63
Male	24 (57)	14 (50)	
Female	18 (43)	14 (50)	
Race: *n* (%)			1.0
White	34 (81)	24 (86)	
Black	3 (7)	2 (7)	
Asian	4 (10)	2 (7)	
Other	1 (2)	0	
Age (years): Mean (SD)	40 (14)	38 (11)	0.48
Comorbid Depression, Current: *n* (%)	5 (11)	5 (17)	0.73

† categorical variables compared with Fisher's Exact test, continuous variables with *t*-test

Table 2

Blood Markers of Acute Stress

	MBSR			SME			*p*-value*
During the TSST	**pre**	**post**	**change**	**pre**	**post**	**change**	
HPA axis markers, mean (SD)							
Cortisol AUC	913 (252)	761 (290)	−152 (256)††	1040 (383)	951 (430)	−89 (328)	0.38
ACTH AUC	1979 (916)	1688 (646)	−290 (541)††	2148 (1145)	2348 (1778)	200 (792)	0.007
Cytokines, mean (SD)							
TNF-alpha AUC	480 (247)	417 (204)	−64 (284)	317 (186)	390 (235)	73 (188)	0.033
IL-6 AUC	157 (145)	120 (114)	−37 (156)	63 (47)	96 (70)	33 (62)†	0.036

p-value of time × treatment type in ANOVA

†within-group comparison of pre-post scores with $p<0.05$,

††within-group comparison of pre-post scores with $p<0.01$