Leg thermotherapy for intermittent claudication

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Statistical Analysis Plan

Demographic and clinical characteristic were summarized overall and by group. Two-sample tests, Wilcoxon Rank Sum test, Chi-square tests, or Fisher's Exact tests were used to compare the two groups. For the analysis of MRI-derived indices, absolute values were used for peak flow and flow per minute as sometimes the values reported from the machine were negative. Percentage change in peak flow is defined as (max absolute value-mean baseline absolute value)/ mean baseline absolute value. For the outcome of 6-min walk test, the best of V1 and V2 was used as baseline. For the MRI-derived indices, the blood parameters, cutaneous microvascular function, and the experimental blood pressure, V2 was used as the baseline; while for the quality of life, V1 was used as the baseline. For physiological variables of systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and temperature in the ear, change from baseline at each time point using the mean of total 18 sessions in two groups was plotted. Area under the curve (AUC), expressed as arbitrary units, for the total 90 minutes was plotted. The AUC for the change from baseline was also plotted in each session in each group. For the cutaneous microvascular function, mean arterial pressure, cutaneous vascular conductance (CVC) and MaxCVC were plotted by mean with standard error at each time point in each experimental visit; AUC for the total 14 time points were also plotted. In the experimental blood pressure, means with standard error were plotted for the change of systolic blood pressure, diastolic blood pressure and mean arterial pressure from baseline timepoint in high-heat therapy group or low-heat therapy group separately; change of AUC in systolic blood pressure, diastolic blood pressure and mean arterial pressure from baseline visit V2 were also plotted. For 6-min walk test, MRI-derived indices, blood parameters, quality of life, the AUC of cutaneous microvascular function indices, and AUC of experimental blood pressure, analyses were done with two different model types. First, linear mixed models with fixed effects for visiting time (V1 or V2, V3, V4) and intervention (high heat, low heat) were fit using the raw data. A significant interaction of time and intervention would indicate that there were differential effects of high and low heat over time. If the interaction was not significant, it was removed. In the main effects only model, a significant main effect for intervention would indicate that the two intervention groups are different (with the same magnitude of difference) across all time points (including baseline). Second, the changes from baseline to V3 and baseline to V4 were modeled with a linear mixed model. Here a significant interaction of time and intervention would mean the intervention effect was different at V3 vs V4. If the interaction was not significant, it was removed. In the main effects only model for change, a significant main effect for intervention would mean that there was an intervention effect, and it was of the same magnitude at V3 and V4. As the results were largely consistent, the results section focuses on the change score model results. Two sample t-tests were used to check whether the AUC for the change of physiological variables were different between two treatment groups. For the cutaneous microvascular function, the MaxCVC from two laser Doppler probes were compared at each timepoint using the linear mixed model with fixed effects for time point and probe, a significant interaction of timepoint and probe would indicate that the MaxCVC from two probes are different over time. The probe effects at each time point were also tested when the probe by time interaction was statistically significant at the significance level 0.05, or the main effects of probe were checked if the probe by time interaction was not statistically significant at the significance level 0.05. All analyses were performed using SAS v9.4.