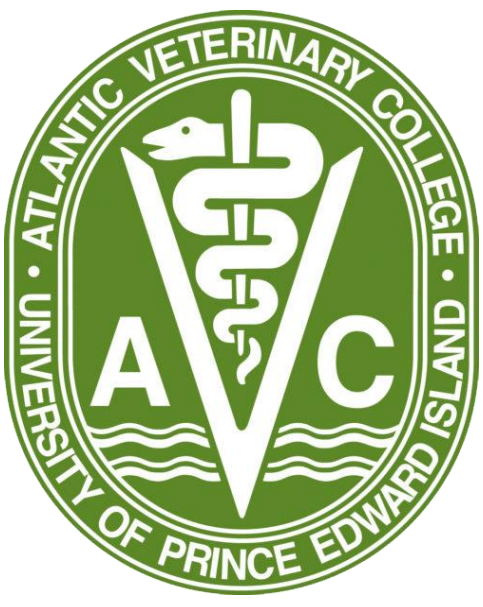




Investigating the Anxiolytic Effects of Pregabalin in Hospitalized Horses

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Introduction

Hospitalization is inherently stressful for horses.¹ Stress can have numerous physiological and behavioral effects and interfere with patient health and welfare.^{2,3} While there are stress-reducing training and environmental modification methods available,^{1,4} they are not always feasible in a hospital setting. Current pharmacological interventions for equines include sedation, acepromazine, and trazodone.⁵ However, these can result in adverse effects, particularly cardiovascular ones, that could limit their use in hospitalized patients.⁵ Pregabalin has been shown to be an effective anxiolytic in humans and small animal species.^{6,7} Pregabalin is used as an analgesic in equine patients and has been shown to have high bioavailability and minimal adverse effects.^{8,9} Previous studies have also suggested that it may have use as an anxiolytic in equines.⁹ However, no studies have been performed to evaluate its anxiolytic effects in horses.

Hypothesis

Horses receiving pregabalin will show significantly lower stress indices during transfer to hospital, admission, and hospitalization than horses receiving a placebo.

Materials and Methods

This study was approved by UPEI's Animal Care Committee.

Fourteen healthy horses were randomly assigned to receive either pregabalin (4mg/kg orally) or a placebo 2 hours prior to hospital admission. To assess stress, heart rate variability (HRV), salivary cortisol, and behavioral scores³ were used. Data was collected under blinded conditions. HRV data was collected at baseline prior to treatment, before and during transfer into the hospital, and after admission (Figure 1). Salivary cortisol samples were obtained at baseline, pre-transfer, and post-admission. Behavioral stress scoring³ was performed at baseline and post-admission.

HRV data was analyzed using Repeated Measures Analysis of Variance (ANOVA). A T test was used to compare each group's difference in mean behavior score between baseline and admission. Significance was set to $p < 0.05$.



Figure 1. Placement of HRV monitor on horse.

Results

Thirteen of 14 horses completed the study. Salivary cortisol analysis remains pending.

When compared using T tests, there were no significant differences found between the 2 groups' mean difference in behavior scores between baseline and admission ($p=0.66$) (Figure 2).

Repeated measures ANOVA analysis of mean HR indicated a difference between mean HR at each time point for the entire sample of horses ($p=0.0004$). A significant time-by-group interaction was also detected ($p=0.0448$), indicating that the mean HR at each time point differed between the pregabalin and placebo groups. While the placebo and pregabalin groups did not significantly differ in mean HR overall ($p=0.4461$), they did differ in how their mean HRs changed over time.

The pregabalin group's mean HR over time graph demonstrated a different shape than the placebo group's (Figure 3). This was also seen for R-R interval over time (Figure 4). In both cases, there was an observed fluctuation of the observation measures of the placebo group that was not replicated in the pregabalin group. The pregabalin group appeared to stay more consistent over time.

Time had a significant effect on R-R interval for both groups ($p=0.0013$), and a time-by-group interaction approached significance ($p=0.0767$).

There were no significant differences between groups for any of the other HRV variables measured, though there was a significant effect of time on Root Mean Square of Successive Differences (RMSSD) for both groups ($p=0.0014$).

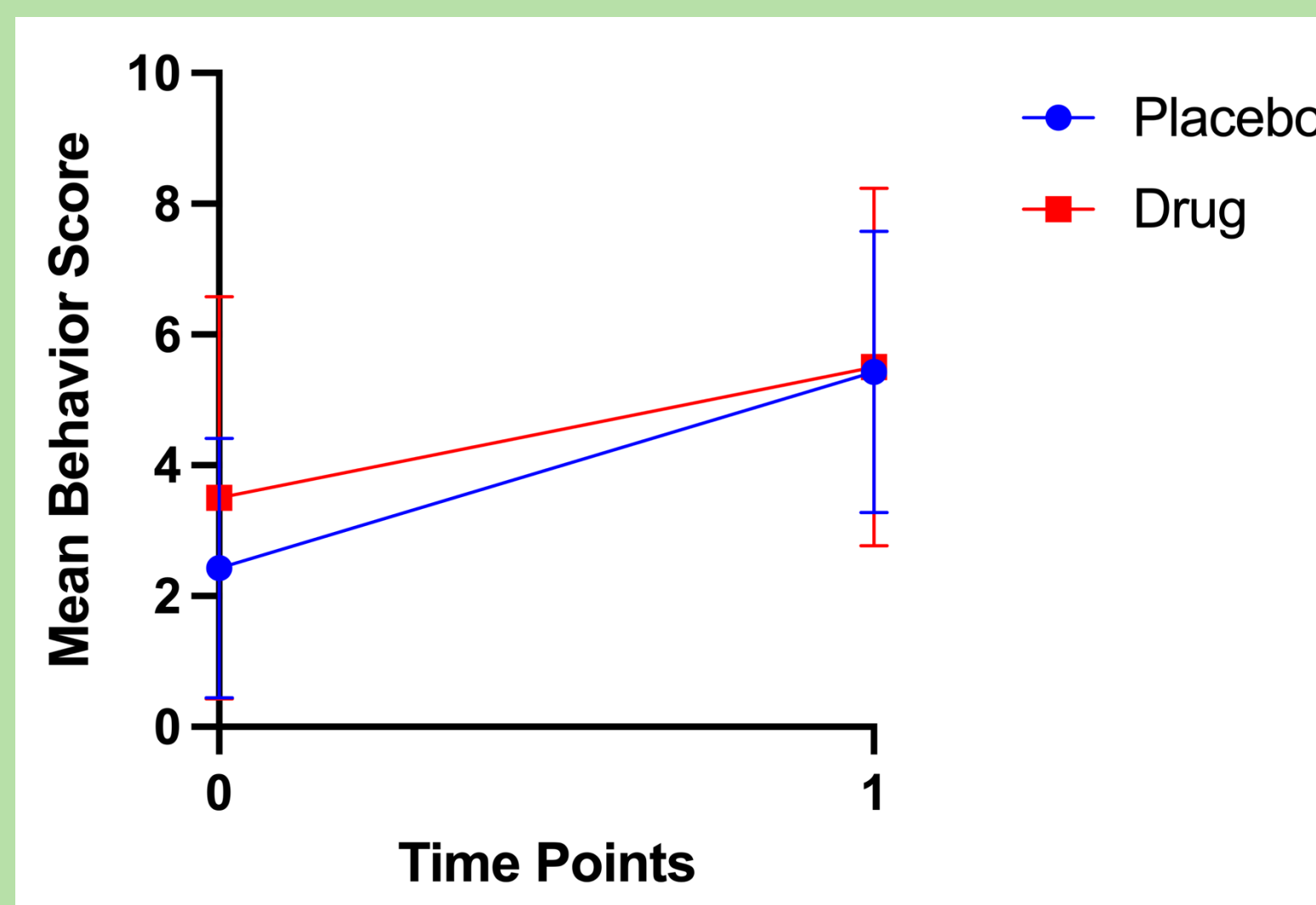


Figure 2. Mean Behavior Score by time point. Time point 0 = baseline, 1 = admission. The 2 groups' mean difference in behavior scores between baseline and admission did not differ significantly.

Figure 3. Mean HR (bpm) by time point. Time point 0 = baseline, 1 = pre-transfer, 2 = transfer, 3 = post-admission. The placebo group showed a large spike in HR at transfer, while the pregabalin group stayed more consistent.

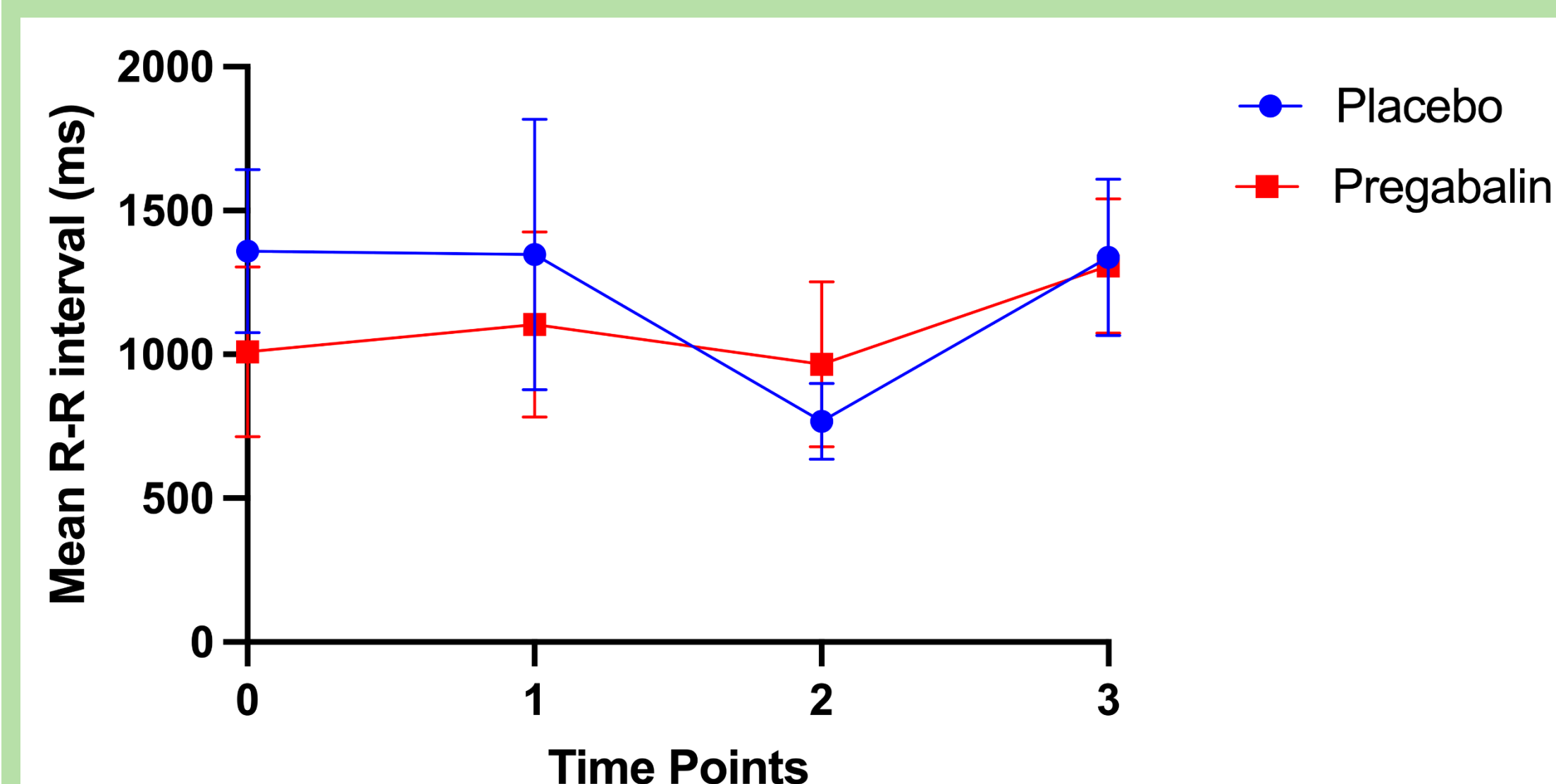
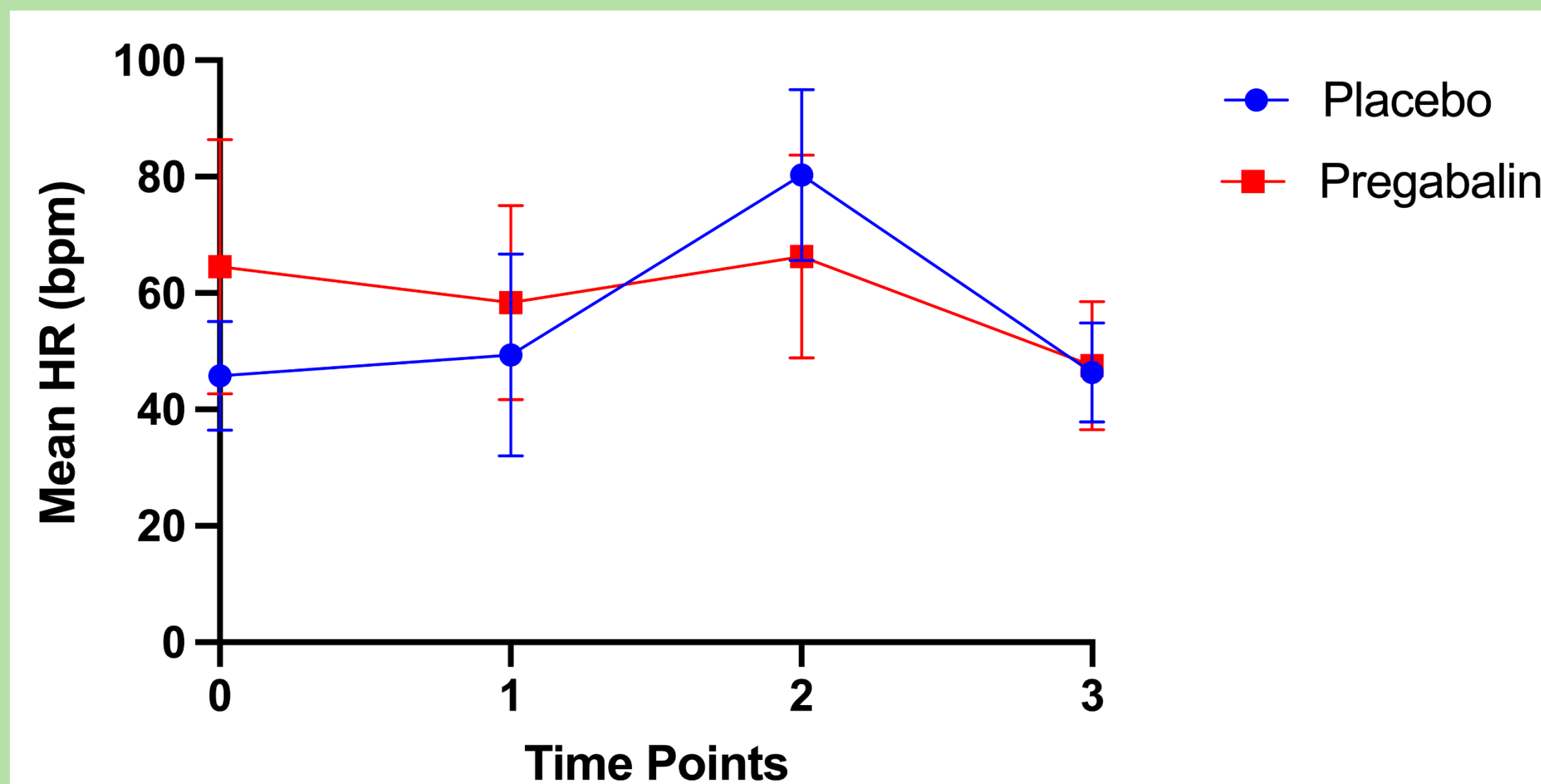


Figure 4. Mean R-R interval (ms) by time point. Time point 0 = baseline, 1 = pre-transfer, 2 = transfer, 3 = post-admission. Time had a significant effect for both groups, and there was a near-significant effect of treatment on this temporal pattern.

Discussion

The pregabalin group's HR and R-R interval appeared to have been more regulated during the study period than the placebo group. Additionally, the significant time-by-group effect found for mean HR supports that the heart rates in the placebo group were more variable when compared to the heart rates in the pregabalin group. This intimates that pregabalin had an effect on HR that the placebo did not, and that pregabalin may help to reduce stress in horses.

One of the major limitations of this data set currently is that the overall study is a crossover design, which is currently proceeding. Thus, the phase 2 data was unavailable for analysis yet and horses had to be compared against each other, rather than against themselves as their own controls. Since each horse experiences unique stress levels with hospitalization, there was a lot of individual variation observed in their responses to handling, transfer, and admission to the hospital. In the future, being able to compare each horse's stress indices when treated with pregabalin vs a placebo will be invaluable. We anticipate finding more significant results once we can use all the data from the crossover phase.

Another limitation of this study is the small sample size limiting statistical power, which we hope to remedy with the crossover portion of this study.

Additionally, salivary cortisol and longer hospitalization timepoint analysis from this phase of the trial are pending and may also influence our conclusions in the future.

Overall, preliminary conclusions from this study indicate that pregabalin may reduce stress in hospitalized horses and could be considered for use as an anxiolytic in equine patients, though further analysis will be critical in reaching more definitive conclusions.

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