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Impact of Midodrine Use on the Hazard of Transfer From the ED

Executive Summary

Midodrine is a drug under consideration for use in the ED to stabilize blood pressure in additional to emergency class vasopressors. The purpose of this study was to assess if midodrine use improves the time to transfer from the emergency department. Using a retrospective cohort of 413 patients followed for two hours after presentation to the ED, transfer times were compared between those who received midodrine and those who did not using a time dependent Cox proportional hazard model. Midodrine use was not found to affect transfer time with a hazard ratio of 0.99 (95% CI 0.77 to 1.29) after controlling for other covariates. Significant predictors of transfer were found to be heart rate, respiratory rate, shock, dehydration, emergency vasopressor type and reason for presentation. Limitations of this study include that it is a retrospective, observational study which cannot fully account for differences between the cohorts and possible lag effects.

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1.0 Introduction

Midodrine is a vasopressor that is typically not used in medical emergencies but instead used to treat chronic orthostatic hypertension. The purpose of vasopressors is to contract the blood vessels resulting in increased blood pressure. Critically low blood pressure is a life-threatening condition that must be addressed in patients who present to the emergency department before they can be transferred. Improving transfer time is highly desirable both for improving the utilization of emergency room resources and for patient outcomes.

It has been suggested that adding midodrine to existing emergency class vasopressors may improve time to stabilization and subsequent transfer time from the ED. Some physicians have been doing this but there is no large-scale examination of the effectiveness of this treatment.

The primary objective of this study is to assess the effectiveness of midodrine on reducing transfer time.

2.0 Methods

2.1 Study Design

This retrospective data set looks at patients who received emergency vasopressors immediately after admission and follows them for two hours after presentation to the ED until they were either transferred or censored. 413 patients were included in the data set. For patients who were given midodrine, the time they started on midodrine and the time they stopped (if applicable) prior to transfer or censoring was recorded.

In addition to the start and stop times of midodrine use and transfer time, patients were assessed for respiratory rate, heart rate, body temperature, age, sex, dehydration, shock, class of emergency vasopressors, reason for presentation to the ER and insurance status.

2.2 Statistical Analysis

Analysis was conducted to determine if the group that received midodrine and the group that didn't varied in terms of any of these covariates. For continuous covariates such as respiratory rate, heart rate, body temperature and age, normality was assessed using histograms, density plots, and Q-Q plots as well as the Shapiro-Wilks test for normality. Group comparisons were made using Wilcoxon Rank Sum tests for non-parametric continuous variables and Pearson Chi-Square tests for categorical variables including dehydration, shock, class of emergency vasopressors, reason for presentation to the ER and insurance status.

The data collected was converted to a time-dependent data set and fit with a Cox proportional hazard model to determine the impact of midodrine on hazard of transfer from the ED. First a univariate cox model with midodrine was constructed to compare midodrine use unadjusted for other covariates. The effect of midodrine was reassessed after considering relevant covariates. The method of p-value screening was used to determine the inclusion of covariates. The only interaction terms screened for inclusion were significant covariates interacting with midodrine use. The model was stratified by sex to account for different baseline hazards between sexes. Model fit was examined by the deviance residuals and the Cox-Snell residuals as well as the test for proportional hazards.

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3.0 Results

3.1 Baseline Characteristics

413 patients were included in the data set. Approximately half (204) received midodrine at some point in the ER and of those 204 patients who started midodrine, 86 of them (42%) stopped receiving midodrine prior to transfer.

Respiratory rate was tested for normality and found to not be normally distributed (Shapiro-Wilk normality test, $p < 0.001$). Heart rate was tested for normality and found to not be normally distributed (Shapiro-Wilk normality test, $p < 0.001$) Temperature was tested for normality and found to not be normally distributed (Shapiro-Wilk normality test, $p < 0.001$). Age was tested for normality and found to not be normally distributed (Shapiro-Wilk normality test, $p < 0.001$). Due to the non-parametric distribution of respiratory rate, heart rate, body temperature and age, group comparisons were made using the Wilcoxon Rank Sum Test. Group proportions for sex, dehydration, vasopressor type, shock and insurance were compared using the Pearson' Chi-Square Test. For all tests, a p value of 0.05 was used for statistical significance.

Table 1 provides a comparison between the group that received midodrine and the group that didn't in terms of patient demographics, clinical presentation and emergency treatment. In terms of patient demographics there were no significant differences between groups in terms of age, sex or insurance status. In terms of clinical presentation, patients given midodrine had a significantly higher respiratory rate ($p=0.005$) and lower heart rates ($p < 0.001$) compared to those who were not given midodrine. Dehydrated patients were more likely to be given midodrine compared to patients who were not dehydrated ($p=0.0134$). Patients in shock were more likely to be given midodrine compared to patients who were not in shock ($p=0.0311$). There were no meaningful differences between groups in terms of body temperature. The distribution of reason for being in the ED differed between patients who received midodrine and those who didn't ($p=0.0261$). Based on inspection of

cell proportions trauma was the most common reason in the no midodrine group (39%) compared to the midodrine group (27%). The distribution of emergency class of vasopressors also differed between patients who received midodrine and those who didn't (p=0. 310). Based on inspection of cell proportions dopamine was the most common emergency vasopressor in the no midodrine group (39%) compared to the midodrine group (29%) and epinephrine was more common (36%) in the midodrine group compared to the no midodrine group (25%).

*Table 1. A comparison of patients who received Midodrine at some point during their time in the ED with those who did not on patient demographics, clinical presentation and treatment. * Indicates statistically significant differences.*

Patient Demographics			
Variable	**Midodrine (n=204)**	**No Midodrine (n=209)**	**p-value**
Age in years, mean (SD)	45.31 (16.64)	46.36 (17.67)	0.5436
Female sex, n (%)	120 (58.8%)	111 (53.1%)	0.2845
No insurance, n (%)	75 (37%)	70 (33.5%)	0.8167
Other insurance, n (%)	21(10%)	26 (12%)	
Private insurance, n (%)	47 (23%)	46 (22%)	
Public insurance, n (%)	61 (30%)	67 (32%)	
Clinical Presentation			
Variable	**Midodrine (n=204)**	**No Midodrine (n=209)**	**p-value**
Respiratory rate, mean (SD)	25.48 (5.72)	23.91 (5.66)	0.0052*
Heart rate, mean (SD)	90.59 (28.48)	106.2 (28.05)	< 0.001*
Body temperature, mean (SD)	37.64 (1.05)	37.74 (1.07)	0.314
Yes Dehydration, n (%)	58 (28.4%)	37 (17.7%)	0.0134*
Yes Shock, n (%)	54 (26.5%)	36 (17.2%)	0.0311*
Reason Medical, n (%)	68 (33.3%)	62 (29.7%)	0.0261*
Reason Other, n (%)	81 (39.7%)	65 (31.1%)	
Reason Trauma, n (%)	55 (27.0%)	82 (39.2%)	
Emergency Treatment			
Variable	**Midodrine (n=204)**	**No Midodrine (n=209)**	**p-value**
Vasopressor Dopamine, n (%)	58 (28.4%)	81 (38.8%)	0.0310*
Vasopressor Epinephrine, n (%)	73 (35.8%)	53 (25.4%)	
Vasopressor Norepinephrine, n (%)	73 (35.8%)	75 (35.9%)	

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3.2 Survival Analysis

Midodrine use was shown to have an unadjusted hazard ratio of 0.91, suggesting that patients who received midodrine were less likely to be transferred out of the ED, however the p-value was 0.419, indicating that this effect was not significant. An unadjusted survival curve comparing midodrine use to no midodrine use appears in Figure 1.

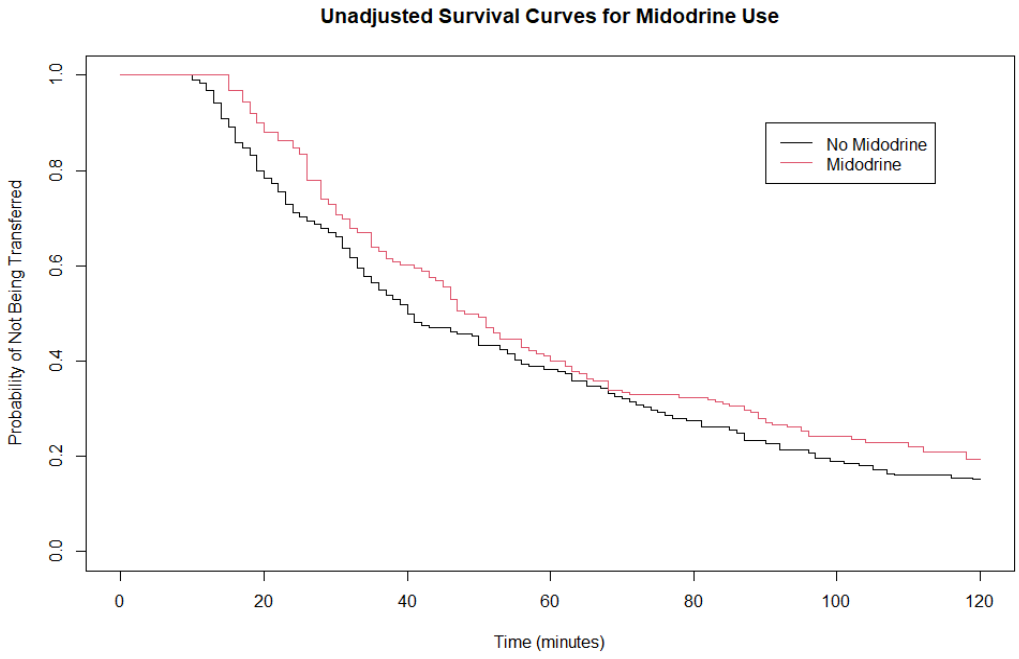

Figure 1. The unadjusted survival curves comparing midodrine use and probability of not being transferred from the ED

The effect of midodrine was reassessed after considering relevant covariates. Statistically significant covariates were determined to be heart rate, respiratory rate, shock, vasopressor type, dehydration and reason for admission. Age, body temperature and insurance status were not significant predictors. The interaction between the significant covariates and midodrine were assessed and no significant interaction effects were found.

The assumption of proportional hazards for each covariate was assessed, and it the model was found to not violate the proportional hazard assumption for any covariates. A summary of the hazard ratios for each covariate can be found in Table 2.

*Table 2. Hazard ratios for relevant covariates in terms of likelihood of transfer from the ED. * indicates reference category as dopamine, ** indicates reference category as medical.*

Variable	**Hazard Ratio**	**95% CI (Hazard Ratio)**	**p-value**
Yes Midodrine	0.9973	(0.7723, 1.2879)	0.9833
Respiratory Rate	0.9595	(0.9410, 0.9785)	< 0.001
Heart Rate	1.0176	(1.0137, 1.0216)	< 0.001
Yes Shock	0.4340	(0.325, 0.5794)	< 0.001
Yes Dehydration	0.5371	(0.4080, 0.7070)	< 0.001
Vasopressor: epinephrine*	0.5864	(0.4449, 0.7729)	< 0.001
Vasopressor: norepinephrine*	0.6105	(0.4719, 0.7900)	< 0.001
Reason: Other**	0.9730	(0.7428, 1.2744)	0.8422
Reason: Trauma**	1.7468	(1.3367, 2.2828)	< 0.001

Midodrine use was not associated with a difference in hazard of transfer (HR: 0.99, 95% CI 0.77-1.28). Heart rate and the reason for admission to the ED being trauma increased the likelihood of transfer from the ED (HR: 1.01 and 1.75 respectively). The reason for admission being other was not considered statistically significant relatively to the reference category of medical. Higher respiratory rates decreased the likelihood of transfer (HR: 0.95, 95% CI: 0.9410 - 0.9785). Shock and dehydration decreased the likelihood of transfer (HR; 0.4340, 95% CI 0.325 - 0.5794 and HR: 0.5371, 95% CI :0.4080 - 0.7070 respectively). Compared to dopamine, epinephrine and norepinephrine decreased the likelihood of transfer (HR: 0.5864, 95% CI: 0.4449 - 0.7729 and HR: 0.6105 95% CI 0.4719 - 0.7900 respectively)

An illustration of the effect of midodrine use can be seen in the survival curves for midodrine use stratified by sex in Figure 2. For these comparisons, quantitative covariates were set to their mean

values, and categorical variables were set to the most common value in the data set. The curve compares survival based on midodrine use in males and females, with a mean respiratory rate of 24.69 breaths per minute, a heart rate of 98.48 bpm, no shock, no dehydration, emergency vasopressor norepinephrine and the reason for presentation as other.

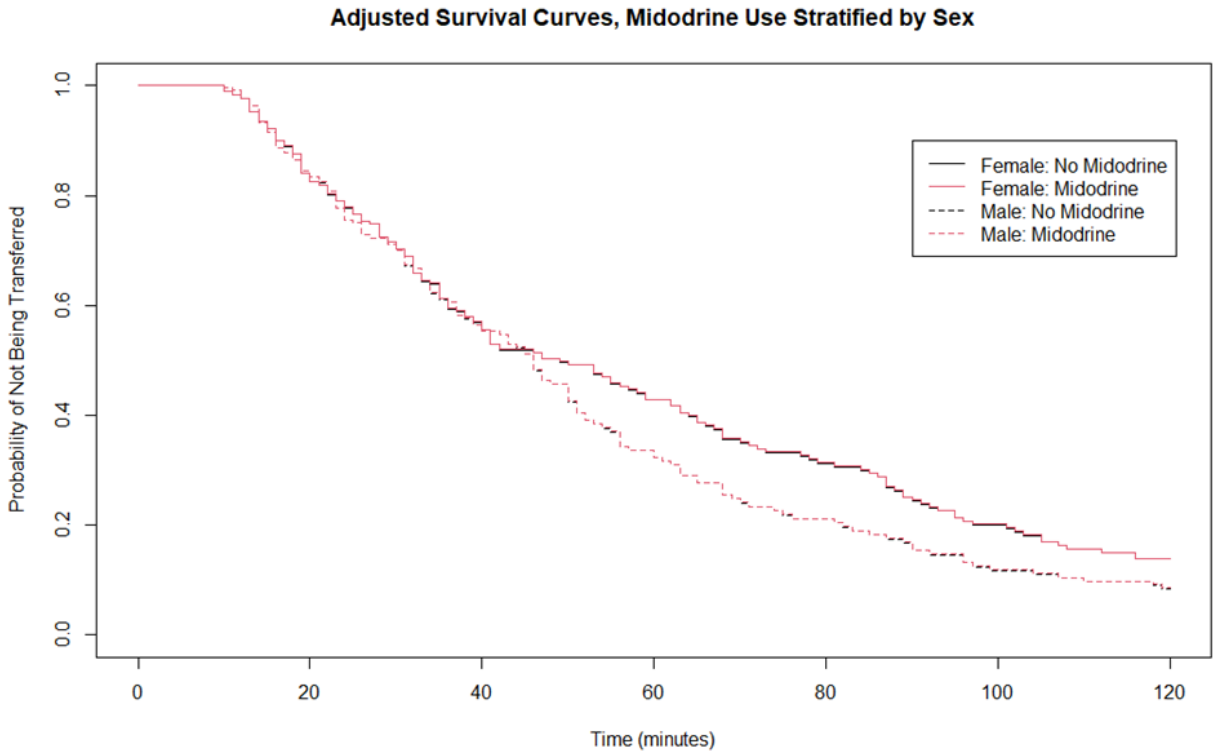

Figure 2. Adjusted survival curves comparing the probability of not being transferred for males and females with and without midodrine use.

3.3 Model Diagnostics

Model fit was examined by the deviance residuals and the Cox-Snell residuals as well as the test for proportional hazards. The proportional hazards assumption was not violated for any covariates. A plot of the deviance residuals appears in Figure 3 showing no indication of significant outliers. The Cox-Snell residuals plotted against the cumulative hazard function and the resulting curve reasonably follows the 45-degree line indicating good model fit (Figure 4.)

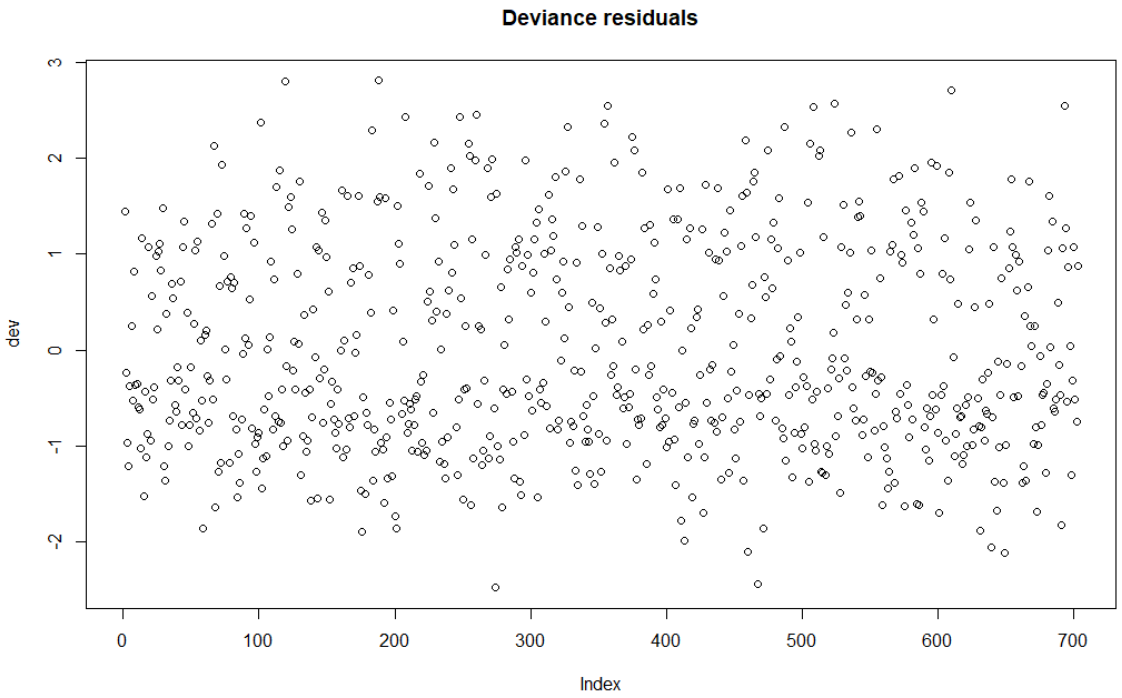

Figure 3 The deviance residuals plot for the final cox model.

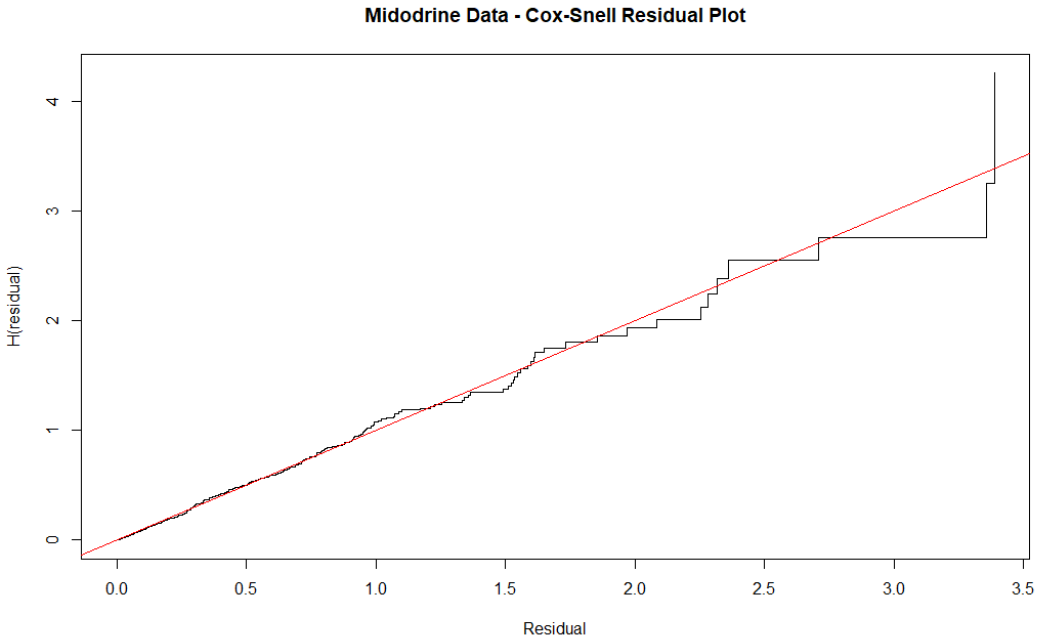

Figure 4. The Cox-Snell residual plot

4.0 Discussion

The goal of this study was to determine the effect of midodrine use on the hazard of transfer from the ED as well as to determine other covariates that impact ED transfer. The findings indicated that midodrine use doesn't impact the hazard of transfer from the ED, but that heart rate, respiratory rate, shock, dehydration, emergency vasopressor type and reason for presentation are significant factors. Interpretation of these results should be done with caution as the study does have significant limitations.

4.1 Limitations

As this is a retrospective, observational, non-randomized study, caution should be used in the interpretation of the results. The the time dependent Cox model created treats midodrine use as a binary variable as a function of time. This statistical treatment measures the effectiveness of midodrine only while in use, ignoring the possibility of lag effects. If a possible lag effect is clinically hypothesized, additional work should be undertaken to compare the outcomes of those who start and stop midodrine with those who do and do not receive it. It should also be noted that there were many significant differences between patients who received midodrine and those who did not. Shock, dehydration and use of emergency vasopressors other than dopamine had a significant negative effect on the likelihood of transfer from the ED and these conditions were more prevalent in those who received midodrine. While the Cox model can account for these variations between groups, they may indicate the presence of other medical factors that may be influencing the hazard of transfer from the ED resulting in confounding by indication. As a result, the effectiveness of midodrine use may be masked due to this source of bias.

4.2 Clinical Implications

These results don't support a clinically meaningful effect on midodrine use in the emergency department setting. This effect was demonstrated both before and after adjustment for relevant

demographic and clinical covariates. It is possible that midodrine is simply too slow acting to be effective within the two-hour window observed in this study.

Baseline differences between the cohort who received midodrine and those who did not suggest higher levels of shock, dehydration, use of epinephrine and norepinephrine in those receiving midodrine. These signs point to clinicians giving midodrine more often to patients who were more unstable. While the Cox model accounts for these factors, it is likely that there is some confounding occurring and the effectiveness of midodrine may be different than what is suggested here.

Another important finding is that several covariates were strongly associated with the likelihood of transfer including heart rate, respiratory rate, shock and dehydration. Higher heart rates, lower respiratory rates (within clinical reason), and treatment of shock and dehydration would all contribute to improved transfer times. Interventions on these symptoms may have a significant positive impact on patient transfer from the emergency department.

It's important to note that midodrine use was not found to be harmful in this data set, despite the absence of a demonstrated benefit. With this in mind, it’s use in the ED may benefit from further study.

4.3 Future directions

Future research should focus on prospective, randomized designs to determine the impact of midodrine use. If clinicians suspect a delayed effect of midodrine, future work should include models that incorporate lagged exposure. Research focused on understanding the decision-making process of physicians when they choose to use midodrine may offer additional insight into sub-groups to investigate and additional paths of analysis.

5.0 Conclusion

This study evaluated the use of midodrine in the emergency department to improve patient transfer times. Midodrine use was not found to be effective at shortening transfer times, even after adjusting for relevant covariates. These findings don't support standard use of midodrine in the emergency department for improving patient transfer times. Prospective, randomized trials as well as models accounting for lag effects may be desirable to better understand the efficacy of midodrine on patient stabilization.