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# Preoperative Midodrine Use Does Not Predict Intraoperative Hypotension During Orthotopic Liver Transplantation

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## Abstract

**Background:** Complications of liver transplantation undermine long term benefits for patients with end-stage liver disease. Some patients awaiting liver transplantation are treated with midodrine, an oral α1 agonist. We hypothesized that preoperative use of midodrine would predict increased intraoperative hypotension with associated vasopressor and blood product administration and deleterious effects on graft survival.

**Methods:** We performed a retrospective, matched case control study examining patients receiving midodrine versus those not before undergoing liver transplantation. Sixty-four patients were examined and analyzed. Primary outcomes were total intraoperative vasopressor use and minutes of intraoperative hypotension.

**Results:** For the primary outcomes, no statistically significant difference was found between the groups. No significant differences were seen in one year patient or graft survival. Statistically significant differences were noted in American Society of Anesthesiologists (ASA) physical status, Model for End-Stage Liver Disease (MELD) scores, preoperative blood pressure metrics, use of continuous renal replacement therapy intraoperatively, cryoprecipitate, and cell saver use.

**Conclusions:** Preoperative use of midodrine in patients undergoing liver transplantation did not predict increased intraoperative hypotension or concomitant need for vasopressors or blood products. Midodrine use was associated with higher ASA and MELD scores, renal replacement therapy, and decreased preoperative blood pressure, but not altered graft survival.

**Keywords:** Midodrine; Liver transplantation; Orthotopic liver transplantation; Transplantation

**Abbreviations:** BMI: Body Mass Index; ASA: American Society of Anesthesiologists; MELD: Model for End-stage Liver Disease; MAP: Mean Arterial Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ERCP: Endoscopic Retrograde Cholangio Pancreatogrphy

## Introduction

End stage liver disease (ESLD) and orthotopic liver transplantation (OLT) are often accompanied by severe derangements in physiologic mechanisms, and pharmacologic interventions are often required to maintain hemodynamic stability. Anesthetic management of OLT can be complicated by multiple factors, including pre-existing hypotension, chronic medications, portal hypertension, ascites, pleural effusion and pulmonary shunting, coagulopathy, renal failure and surgical manipulations.

Hypotension is a common finding in patients awaiting liver transplantation. The pathophysiology underlying hypotension in ESLD is complex, but it has been noted that excessive nitric oxide production with subsequent vasodilation and activation of the renin-angiotensin-aldosterone system plays a role [1,2]. A pharmacologic intervention employed to counter hypotension in these patients is midodrine [3]. Midodrine is a direct acting α1-adrenoceptor agonist which causes venous and arterial vasoconstriction through stimulation of α1-receptors located in the vasculature. The net result is an increase in vascular tone and systolic blood pressure. Cardiac β-receptors are unaffected and there is no significant blood brain barrier penetration. In healthy patients, an oral dose of 10 mg can increase the blood pressure 10-30 mmHg at 1 hour and remain elevated for another 3-4 hours [4]. Midodrine has been studied in patients with hepatorenal syndrome and cirrhosis, hemodialysis induced hypotension, spinal cord injury and orthostatic hypotension [5-9], but our review of the existing literature revealed scant data on midodrine use and any associated effects on liver transplantation [10].

We hypothesized that patients undergoing liver transplantation while on midodrine might have significantly more challenging intraoperative courses and adverse outcomes postoperatively; and therefore, midodrine use could serve as a marker for increased perioperative risk in liver transplantation. Clinically, we hypothesized that intraoperative hypotension would be more pronounced in patients on midodrine and they would require increased vasopressors. Additionally, they would likely require more intravenous fluids and blood products and have more tumultuous postoperative courses with potentially deleterious effects on graft outcomes.

## Methods

After Institutional Review Board approval, we utilized a retrospective, matched case control design examining patients taking midodrine preoperatively versus those not taking midodrine who had undergone liver transplantation at our institution. The electronic medical record database was queried for patients who had undergone liver transplantation from 1 September 2010 through 30 June 2015, and patients were sorted into those receiving midodrine pre-transplant versus those not taking midodrine. During the study period our query extracted 324 total patients. Fifty of these were taking midodrine before receiving their transplant.

After de-identifying all patients, the midodrine cohort was demographically paired with control patients using age, gender, BMI, and donor type (live *vs.* deceased) to minimize confounding variables. This resulted in thirty-three demographically matched pairs. Once the two groups were finalized, the patients' medical records were reviewed by blinded reviewers and the pre-determined data points were collected (Table 1). Manual chart review was performed to verify the automatically collected data as well as to supplement any missing variables. During review of the medical records, one patient pair was removed from the study due to midodrine use only during dialysis, while all other midodrine patients were receiving midodrine daily. Dosing varied for the patients taking midodrine. The range was 2.5 mg TID to 15 mg TID. Two patients were on 2.5 mg TID, six were on 5 mg TID, nineteen were on 10 mg TID, and five were on 15 mg TID. The final analysis consisted of thirty-two matched pairs for a total sample size of sixty-four patients. After primary statistical analysis, a regression analysis was performed utilizing MELD-matched controls to re-assess outcomes when patients' MELD scores were included in the analysis.

**Patient characteristics**

- Age
- BMI
- Gender
- ASA physical status score
- MELD score
- Etiology of liver disease
- Donor type
- Midodrine use/dose

**Perioperative data**

- Intraoperative continuous renal replacement therapy use
- Intubation time (hours)
- Length of hospital stay (days)
- Preoperative blood pressure
- Minutes of intraoperative hypotension
  - <70 mmHg
  - 70-79 mmHg
  - 80-90 mmHg
- Surgery duration (hours)
- Total intraoperative vasopressor dosing
  - Ephedrine (mg)
  - Epinephrine (mcg)
  - Norepinephrine (mcg)
  - Phenylephrine (mcg)
  - Vasopressin (units)
- Total intravenous fluid and blood products (ml)
  - Cell Saver
  - Colloids
  - Cryoprecipitate
  - Crystalloids
  - Fresh frozen plasma
  - Packed red blood cells
  - Platelets

**Patient/graft long term data**

- 'Bring back' surgery (return to OR within one week of transplantation)
- Death (within twelve months of transplantation)
- ERCPs performed (within twelve months of surgery)
- Total surgical procedures performed (within twelve months of surgery)

**Table 1:** Data points collected.

### Statistical methods

Once all data was collected, statistical analyses were performed using the statistical software package SAS Studio 9.3 (SAS Institute, Cary, NC). Descriptive summaries such as mean, median, standard deviation, and range are provided for quantitative variables, along with frequencies and percentages for categorical data. The p-values resulting from the comparison between the two groups cases vs. controls were based on running a conditional logistic, in order to account for the clustering due to matching the cases vs. controls. The condition logistic regression model included the grouping factor (cases vs. control) and the risk factor MELD score. The significance level was at 0.05.

## Results

Intraoperative vasopressor use and total minutes of intraoperative hypotension were not found to be statistically different between the two cohorts in both the primary analysis (Tables 2A and 2B) and in the regression analysis utilizing MELD scores (Table 3). Intraoperative hypotension was defined as total minutes with systolic blood pressures recordings under 90 mmHg with subset analysis of recordings under 80 and 70 mmHg respectively. Vasopressor use included comparison of ephedrine, epinephrine, norepinephrine, phenylephrine, and vasopressin.

| | Control (n=32) | Midodrine (n=32) | Total (n=64) | p-value |
|---|---|---|---|---|
| Age | 56.4 | 55.9 | 56.2 | |
| BMI | 27.4 | 26.8 | 27.1 | |
| ASA score | 3.4 | 3.9 | 3.7 | 0.0083 |
| MELD score | 26.4 | 34.9 | 30.6 | 0.0024 |
| Crystalloids (ml) | 5130.6 | 5339.9 | 5235.3 | 0.8306 |
| Colloids (ml) | 875.1 | 999.9 | 937.5 | 0.6216 |
| Cell saver (ml) | 312.2 | 882.9 | 597.6 | 0.0308 |
| Packed red blood cells (ml) | 1816.5 | 2561.9 | 2189.2 | 0.2727 |
| Cryoprecipitate (ml) | 162.6 | 308.7 | 234.5 | 0.0369 |
| Platelets (ml) | 274.3 | 384.3 | 328.4 | 0.2473 |
| Fresh frozen plasma (ml) | 1012.4 | 1400.7 | 1206.5 | 0.2520 |
| Epinephrine (mcg) | 631.9 | 722.5 | 677.2 | 0.7651 |
| Norepinephrine (mcg) | 193.8 | 506.3 | 347.6 | 0.2321 |
| Phenylephrine (mcg) | 5961.3 | 8141.0 | 7051.2 | 0.3743 |
| Ephedrine (mg) | 12.5 | 51.9 | 32.5 | 0.5007 |
| Vasopressin (units) | 21.0 | 83.7 | 52.4 | 0.4924 |
| Preoperative MAP (mmHg) | 84.2 | 71.2 | 77.7 | 0.0107 |
| Preoperative SBP (mmHg) | 122.2 | 106.3 | 114.3 | 0.0196 |
| Preoperative DBP (mmHg) | 66.5 | 54.8 | 60.6 | 0.0084 |
| Intraoperative SBP <70 mmHg (mins) | 9.7 | 8.2 | 8.9 | 0.7262 |
| Intraoperative SBP 70-79 mmHg (mins) | 17.7 | 18.3 | 18.0 | 0.9025 |
| Intraoperative SBP 80-90 mmHg (mins) | 42.1 | 59.7 | 50.9 | 0.2448 |
| Surgical duration (mins) | 268.9 | 258.1 | 263.6 | 0.4095 |
| Time to extubation (hours) | 27.3 | 30.5 | 28.9 | 0.5043 |
| Length of hospital stay (days) | 10.8 | 12.6 | 11.7 | 0.5318 |
| Total surgical procedures within 12 months | 2.1 | 1.8 | 2.0 | 0.6850 |
| # ERCPs within 12 months | 1.4 | 0.9 | 1.2 | 0.3104 |
| Data summary showing mean values for control group, midodrine group, and total for selected data points. | | | | |

**Table 2A:** Data Analysis.

| | Control (n=32) | Midodrine (n=32) | Total (n=64) | p-value |
|---|---|---|---|---|
| Male gender | 18 | 18 | 36 | |
| ASA emergency status | 11 | 17 | 28 | 0.1657 |
| Intraoperative CRRT | 4 | 22 | 26 | <0.0019 |

| | | | | |
|---|---|---|---|---|
| Bring back to OR within 1 week | 5 | 4 | 9 | 0.7064 |
| ERCP within 12 months | 14 | 8 | 22 | 0.1214 |
| Required other surgical procedures within 12 months | 11 | 18 | 29 | 0.1000 |

**Table 2B:** Data Analysis.

| | Primary analysis p-value | Regression analysis p-value |
|---|---|---|
| ASA Score | 0.0083 | 0.1465 |
| CRRT | 0.0019 | 0.0366 |
| Cell Saver | 0.0308 | 0.0522 |
| Cryoprecipitate | 0.0369 | 0.3516 |
| Preoperative SBP | 0.0196 | 0.0953 |
| Preoperative DBP | 0.0084 | 0.0655 |
| Preoperative MAP | 0.0107 | 0.0711 |
| Extracted metrics from regression analysis using MELD scores to match patients with updated p-values for selected metrics. Notice that in regression analysis only intraoperative CRRT remained statistically significant with a p-value <0.05. All omitted metrics remained statistically non-significant with p-values>0.05. | | |

**Table 3:** Primary versus Regression Analysis.

In the initial demographically matched cohort analysis, statistical significant differences were noted in secondary metrics including: ASA physical status, MELD scores, all preoperative blood pressure recordings (systolic, diastolic, and mean arterial pressures), use of continuous renal replacement therapy (CRRT) intraoperatively, cryoprecipitate use, and cell saver use. Midodrine patients had mean ASA scores of 3.9 compared to 3.4 for the control group (p=0.008, SD 0.5 and 0.4 respectively). Mean MELD scores were 26.3 for the control group versus 34.9 for the midodrine group (p=0.003, SD 8.3 and 9.1 respectively). The midodrine group's preoperative blood pressure was appreciably lower, despite the effects of midodrine: mean arterial pressure was 68.8 mmHg for the midodrine group compared to 82.0 mmHg for control group (p=0.0005, SD 10.0 and 15.6 respectively). Additionally, 68.8% of the midodrine group required CRRT intraoperatively compared to 12.5% of the control group. Lastly, the midodrine group required more cryoprecipitate and cell saver products when compared to their matched pairs, but not other fluid or blood products. Midodrine patients received a mean of 883 ml of cell saver products while the control group had a mean of 312 ml. For cryoprecipitate, the midodrine group received a mean of 309 ml compared to 163 ml for the control group.

To account for MELD scores not included in the initial demographic pairing, we performed a regression analysis using MELD scores and found utilization of CRRT to remain a statistically significant difference between the cohorts with a p-value=0.036 while all other metrics failed to meet statistical significance. With the regression analysis, differences in ASA physical status, preoperative blood pressure recordings, cryoprecipitate use, and cell saver use were no longer noted.

To assess for post-operative complications we examined 'bring-back' surgery in the first week post-operatively, number of post-transplant endoscopic retrograde cholangiopancreatography procedures (ERCP), total number of surgical procedures, graft survival, and patient survival in the twelve months following transplantation. In none of these metrics did we appreciate a statistical difference. No patients were deceased within twelve months in the midodrine group and two patients were deceased in the control group. Of the deceased patients, one had a fatal intracranial bleed while the other died of complications following tacrolimus toxicity and multisystem organ failure.

## Discussion

Liver transplantation is often the final treatment option for patients with acute liver failure, end-stage liver disease, and primary hepatic malignancy. The physiologic sequelae of liver disease are numerous and guide transplantation decisions as liver transplantation is not without significant risks which must be weighed against the benefits of the procedure.

Compounding the challenge of liver disease are the immediate complications associated with liver transplantation. The perioperative management of liver transplantation requires aggressive medical optimization. Anesthetic management of the intraoperative portion often necessitates significant fluid resuscitation with concomitant vasopressor and blood product utilization. However, there is considerable variation in perioperative challenges between patients and markers providing predictive value are lacking.

Midodrine has been studied in hepatorenal syndrome and cirrhosis, orthostatic hypotension, hemodialysis, and in spinal cord injuries [5-9,11-14]. As a α1 agonist available in oral formulation, midodrine is utilized as a vasopressor agent. Its current FDA indication is for the treatment of symptomatic orthostatic hypotension in doses of 5-10 mg every 3-4 hours while the patient is upright and a maximum daily dose of 30 mg [4]. Off-label uses include vasovagal syncope, hepatorenal syndrome, prevention of hypotension associated with hemodialysis, and in spinal cord dysfunction. In cirrhotic subjects midodrine has been utilized to mitigate renal function and optimize sodium excretion [15].

We hypothesized that preoperative midodrine use would predict increased intraoperative hypotension. This hypothesis was supported by the statistically significant decrease in systolic, diastolic, and mean arterial pressures preoperatively in the midodrine cohort despite midodrine use. However, we did not find a significant difference in intraoperative hemodynamics. Furthermore, we did not find a significant difference in vasopressor use, colloid or crystalloid administration, or blood product utilization with the exception of cell saver and cryoprecipitate. It is unclear why the midodrine subjects received more cell saver and cryoprecipitate while not requiring significant increases in other fluid or blood products. In regression

analysis utilizing MELD scores to match the comparative groups, this difference was not noted. Comparison of the requirements for fluid resuscitation, blood products, and vasopressor therapy does suggest an overall trend towards increased fluid, blood product, and vasopressor need in the midodrine group; however this did not meet the threshold for statistical significance.

While we found midodrine use associated with higher ASA and MELD scores and the need for renal replacement therapy in demographically paired patients, it did not predict adverse intraoperative or post-operative outcomes in our patients. Indeed, our study participants were matched based on demographic data rather than ASA or MELD scores, and in spite of the elevated ASA and MELD scores for the midodrine group, they did not have increased intraoperative hypotension, increased utilization of vasopressor agents, or increased resuscitative needs. Furthermore in our study, patients did not have notably increased postoperative complications. We hypothesized that midodrine would predict more tumultuous perioperative hemodynamics and yet found minimal differences between the two groups despite the disparate ASA and MELD scores. Indeed, with regression analysis of the data using MELD scores, the outcomes remained unchanged with no significant difference between the groups in intraoperative or post-operative metrics. Due to technical and statistical limitations in the number of patients available in our database, we were unable to match patients based on MELD scores initially for this study and instead had to perform regression analysis to account for the impact of MELD scores in our comparisons.

Ultimately, the only metric found to be consistent in the initial analysis and in the regression analysis was the need for intraoperative continuous renal replacement therapy (CRRT). Likely, the association of midodrine and the need for intraoperative CRRT is driven more by the pre-existing need for renal replacement therapy than midodrine predicting the need for renal replacement therapy. There is well documented benefit from midodrine therapy while on renal replacement therapies [5,9,16]. Hemodialysis often produces hypotension as a portion of a patient's intravascular volume is removed from the effective circulation during dialysis. The addition of midodrine is one therapeutic intervention employed to elevate blood pressure so hemodialysis is hemodynamically tolerated by these patients. The finding that our midodrine group was more likely to undergo intraoperative continuous renal replacement therapy is not surprising since many of the patients were likely started on midodrine in conjunction with preoperative hemodialysis.

Medical literature database searches reveal minimal studies assessing midodrine directly in relation to OLT. Several studies have examined the outcomes of OLT when patients with hepatorenal syndrome are treated with midodrine, but to our knowledge none have directly assessed the perioperative impact of midodrine on OLT [12,17].

Limitations of our study include the relatively small size of the study population. Identifying an adequate number of patients undergoing OLT on midodrine and then pairing them with a demographically matched cohort yielded thirty-two matched pairs. Obviously, the statistical yield of our data would be improved with a larger sample population. As mentioned above, a slight trend towards increased requirements for fluid, blood, and vasopressor products might have become statistically significant with a larger study population. Midodrine dosing was varied among our patients and given the relatively small sample size; we were unable to stratify patients based on their midodrine dosing. Additionally, this was a single center study which potentially introduces bias based on institutional practice standards. Furthermore, the study is a retrospective, matched case control study which inherently carries the risk of potential confounding factors distorting the data.

For our matching process, we focused on demographic data points to pair the midodrine patients with non-midodrine patients. Alternatively, we could have selected MELD or ASA scores to stratify our patients. Our focus on demographic data points (age, gender, donor type, and body mass index) was to account for important factors when comparing OLT patients that are not directly assessed in MELD and ASA scores. Importantly, the matching process was limited by the original population of fifty OLT patients on midodrine preoperatively and as additional variables were employed in the matching process, the total number of study patients successfully matched decreased. Ultimately, the four metrics listed above were selected as an appropriate balance between demographic matching and adequate sample size. To account for not using MELD scores to match patients, we ran a regression analysis as discussed previously.

In conclusion, preoperative use of midodrine in patients undergoing liver transplantation did not predict increased risk of intraoperative hypotension or concomitant need for vasopressors or blood products. Midodrine use was associated with higher ASA and MELD scores, renal replacement therapy, and decreased preoperative blood pressure. Regression analysis examining MELD scores was significant for increased intraoperative CRRT among the midodrine patients, but otherwise revealed no significant differences between the cohorts. No effect was detected on longer term outcomes such as one year patient and graft survival. Identifying factors predictive of perioperative and long term transplantation success are crucial as concomitant advances are made in other aspects of transplantation. Refining the precise role of midodrine in OLT will require additional prospective studies.

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## Conflicts of Interest

None

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