PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLES

Incidence of Rebound Hypertension after Discontinuation of Dexmedetomidine

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INTRODUCTION To date, no studies have evaluated the incidence of rebound hypertension occurring with the discontinuation of long-term (> 72 hrs) dexmedetomidine infusions. Rebound hypertension has been documented in the literature with clonidine, a structurally and pharmacologically similar medication.

OBJECTIVES To compare the incidence of rebound hypertension associated with cessation of dexmedetomidine infusion with other sedative medications.

METHODS This retrospective, matched cohort study evaluated the incidence of rebound hypertension in intensive care unit patients receiving continuous infusions of at least 72 hours in duration of dexmedetomidine, propofol, or midazolam.

RESULTS The study population consisted of 216 patients: 54 treated with dexmedetomidine and 162 treated with propofol or midazolam. Rebound hypertension occurred significantly more often in patients with a history of hypertension (71.1%) than in patients with no prior hypertension (28.9%; $p<0.001$).There was no difference in incidence of rebound hypertension in the dexmedetomidine or propofol and midazolam arms (16.7% vs 17.9%, $p=0.837$). The titration timeframe for the dexmedetomidine infusion, defined as the time from peak infusion rate until discontinuation, was significantly shorter in patients with rebound hypertension (median duration, 4 hrs) compared with patients who did not have rebound hypertension (median duration, 17 hrs; $p=0.011$).

CONCLUSION There was no difference in the incidence of rebound hypertension observed with dexmedetomidine discontinuation compared with propofol or midazolam. Instead, history of hypertension and a shorter weaning duration appear to be associated with increased risk of rebound hypertension regardless of the sedative used.

KEY WORDS dexmedetomidine, withdrawal, hypertension, rebound hypertension.

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Dexmedetomidine is a selective, centrally acting alpha-2 adrenergic agonist that is structurally and pharmacologically similar to clonidine. However, dexmedetomidine is 8-fold more specific for the 2a subtype of the central alpha-2 adrenergic receptor than clonidine.[1] Rebound hypertension can occur with abrupt discontinuation of clonidine, and tapering of the dose is recommended when therapy is discontinued. Rebound hypertension has been reported during the initiation of transdermal clonidine and immediately following discontinuation.[1, 2] This phenomenon is thought to be due to a large catecholamine release after the removal of the inhibitory effects of clonidine on the sympathetic nervous system. Because of

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structural and pharmacological similarities with clonidine, the prescribing information for dexmedetomidine includes a warning to avoid abrupt discontinuation in order to avoid rebound hypertension, though published accounts are limited to case reports.

Rebound hypertension has not been reported in randomized controlled trials comparing dexmedetomidine to benzodiazepines or propofol.[3–6] A 2014 study that compared the incidence of hypotension, hypertension, and bradycardia with dexmedetomidine infusion within 24 hours and beyond 24 hours found no significant differences in adverse events or evidence of withdrawal syndrome.[7] Herein, we report the findings of our study designed to determine if rebound hypertension occurs more frequently after dexmedetomidine discontinuation than after discontinuation of other continuously infused sedative medications.

Methods

Records for all critically ill patients older than 18 years who were admitted to the surgical intensive care unit (ICU), medical ICU, trauma/burn ICU, or neurocritical care unit at Michigan Medicine between June 1, 2014, and June 1, 2017, were reviewed for inclusion in the study. Eligible patients received at least 72 hours of continuously infused dexmedetomidine, propofol, or midazolam for ICU sedation. Sedative selection was at the discretion of the ICU team. Generally, sedative selection at our institution is guided by the recommendations of the Society of Critical Care Medicine guidelines on pain, agitation, and delirium. Some variation exists between units and providers, but propofol is the preferred first-line agent for most patients. Patients were excluded if they had received these medications for other indications, such as alcohol withdrawal or status epilepticus, or if a combination of sedatives was simultaneously administered. We matched patients in a 3:1 manner between the control group (propofol or midazolam) and the study group (dexmedetomidine) based on whether they had a history of hypertension.

The primary outcome was incidence of rebound hypertension after cessation of dexmedetomidine infusion compared to the control group. Rebound hypertension was defined as receipt of an antihypertensive medication in response to hypertension or reinitiation of dexmedetomidine infusion due to hypertension within 24 hours of discontinuation. Nursing documentation of blood pressure and Richmond Agitation Sedation Scale scores were assessed to ensure that the indication for reinitiation of dexmedetomidine was hypertension rather than isolated agitation. Secondary outcomes included the effects of cumulative dose and duration of dexmedetomidine on the incidence of rebound hypertension and subgroup analyses of those same outcomes between patients with and those without a history of hypertension.

Statistical analyses were performed using SPSS version 24. Categorical variables were analyzed with Pearson Chi-square test, and continuous variables were analyzed with Student's *t* test and Mann–Whitney *U* where appropriate. Analyses for primary, secondary outcomes, and subgroup comparisons assumed a two-sided significance level of 0.05.

Results

The study population consisted of 216 patients who received dexmedetomidine (n=54) or propofol or midazolam (n=162) (Figure 1). One hundred seventy-six patients received dexmedetomidine and 122 were excluded, largely due to a duration of therapy < 72 hours. Baseline characteristics were similar between the groups, including severity of illness at admission, age, and gender (Table 1).

There was no difference in the rates of rebound hypertension between the study group and the control group (Table 2). Rebound hypertension occurred in 16.7% (n=9) patients in the dexmedetomidine group and 17.9% (n=29) patients in the control group (p=0.837). Patients in the dexmedetomidine group with rebound hypertension had a median infusion duration of 77 hours (75–94.5 hrs) compared to 114 hours (101–143 hrs) in patients without rebound hypertension (p=0.01). Among the nine patients in the dexmedetomidine group with rebound hypertension, 77.8% (n=7) had a documented history of hypertension, whereas 69% (n=20) of patients in the control group with rebound hypertension had a history of hypertension (p=0.48). Of the 45 patients who received dexmedetomidine who did not have rebound hypertension, 33.3% (n=15) had a documented history of hypertension.

There was no difference in the cumulative dose (expressed as either total dose or weight-based dose per day) of dexmedetomidine among patients with rebound hypertension versus patients without rebound hypertension (Table 2).

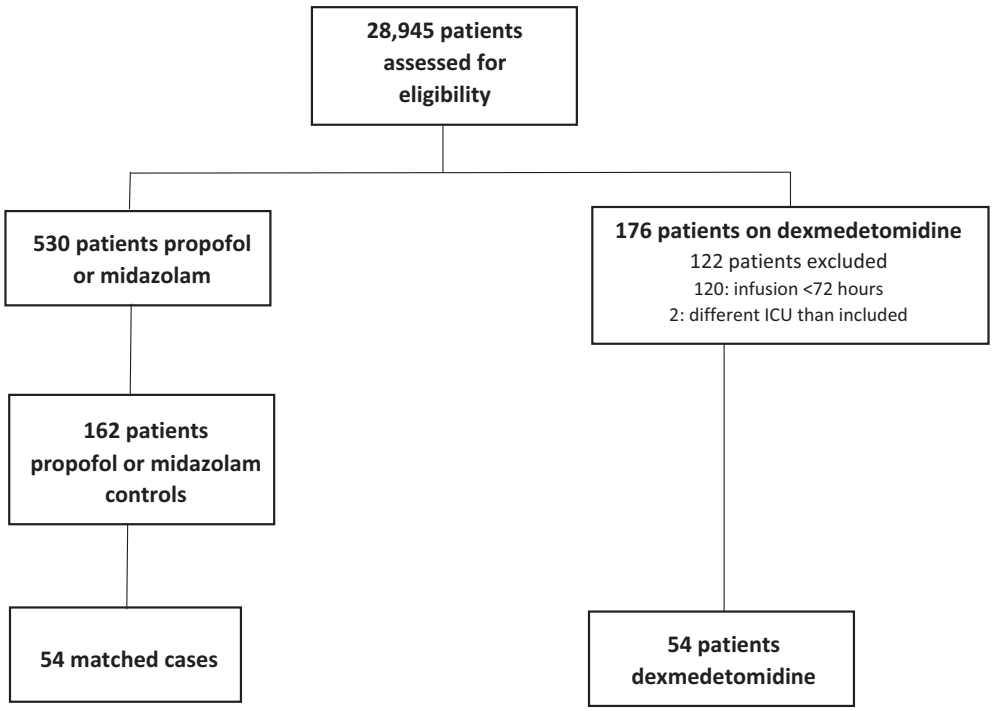

Figure 1. Trial profile.

Table 1. Baseline Characteristics

Baseline Characteristics	Dexmedetomidine Arm (n=54)	Propofol or Midazolam Arm (n=162)	p-Value
Age, median (IQR) yrs	49 (33.25–66.75)	55.5 (39.5–66)	0.508
Male, n (%)	33 (61.1)	81 (50)	0.269
Hypertension history	22 (40.7)	66 (40.7)	1.00
Unit, n (%)			
MICU	30 (55.6)	91 (56.1)	0.863
NCCU	3 (5.6)	7 (4.3)	
SICU	13 (24)	32 (19.8)	
TBICU	8 (14.8)	32 (19.8)	
Length of stay, median (IQR) days	27.5 (20.25–45.75)	26 (16–41)	0.161
APACHE III score, median (IQR)	80 (56–88)	67 (49–80)	0.187

APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range; MICU = medical intensive care unit; NCCU = neurocritical care unit; SICU = surgical intensive care unit; TBICU = trauma and burn intensive care unit.

Discussion

A withdrawal syndrome after dexmedetomidine discontinuation has been reported in pediatric patients, though hypertension was accompanied by other symptoms of withdrawal including emesis and tachycardia.[8, 9] In one of the cases, withdrawal from opiates and/or benzodiazepines may have contributed to the symptoms.[8] Researchers[10] reported two cases of possible dexmedetomidine withdrawal in adult patients who developed hypertension, tachycardia, and agitation. The patients received dexmedetomidine for approximately 144 and 168 hours with infusion rates of up to 1.4 mcg/kg/hour. One patient experienced mydriasis and diaphoresis.

Ours is the first comparative study to evaluate the risk of rebound hypertension after dexmedetomidine discontinuation. Our analysis demonstrated that patients who received continuous infusions of dexmedetomidine were not more likely to experience rebound hypertension than patients who received other continuously infused sedatives. Instead, patients with a prior history of hypertension were more likely to experience rebound hypertension regardless of the type of sedative used. Indeed, in the dexmedetomidine cohort, 47% of patients with a history of hypertension experienced rebound

Table 2. Endpoints

Primary Endpoint			
	Dexmedetomidine Arm (n=54)	Propofol or Midazolam Arm (n=162)	p-Value
Incidence of rebound hypertension, n (%)	9 (16.7)	29 (17.9)	0.837

Secondary Endpoints and Subgroup Analyses			
Dexmedetomidine Arm	Rebound Hypertension (n=9)	No Rebound Hypertension (n=45)	p-Value
Amount of dexmedetomidine, median (IQR) mcg	3354.4 (2785.6–6061.6)	7528.4 (3804.8–10,730.8)	0.072
Amount of dexmedetomidine, median (IQR) mcg/kg/day	13.21 (11.09–15.76)	14.23 (8.14–23.58)	0.880
Duration of dexmedetomidine, median (IQR) hrs	77 (75–94.5)	114 (101–143)	0.01
Time from peak infusion rate to discontinuation, median (IQR) hrs	4 (3–10)	17 (8–32)	0.011
Amount of infusion time with appropriate awakening trials, median (IQR) percentage	33.3 (14.3–33.3)	40 (14.3–50)	0.367

IQR = interquartile range.

compared to 6.6% of patients without a history of hypertension. Similarly, 43% of patients in the propofol and midazolam group who had a history of hypertension experienced rebound compared to 10% without a hypertension history. These findings highlight the need for clinicians to appreciate a patient's prior hypertension history in order to carefully titrate sedation or reinstitute antihypertensive therapy. Last, the duration of dexmedetomidine infusion did not influence occurrence of rebound hypertension suggesting that drug exposure may not predict the likelihood of this adverse event. The lack of difference in cumulative dose between those two subgroups supports that notion.

Though total drug exposure may not be related to the likelihood of rebound hypertension, it is possible that discontinuing the medication too quickly may be harmful. Certainly that is the implication of the warning in the package labeling. From a retrospective perspective, it was expectedly difficult to assess motivation, intention, or strategy underlying decisions about the method of discontinuing dexmedetomidine.

The interpretation of our data is limited by its retrospective nature. It is possible that documentation of preexisting hypertension or reporting of infusion rates or vital signs could be incomplete. Also, we are limited to reporting clinical practice as it is, rather than the effects of rigorously controlled sedation strategies with predefined titration and weaning that one might find in a prospective, randomized study. Physician prescribing preferences also may have led to differences in baseline characteristics. Nonetheless, our study refines our understanding of dexmedetomidine discontinuation. The risk of postdiscontinuation rebound hypertension is no different with dexmedetomidine than alternate sedatives. However, patients with a history of hypertension may be at higher risk. A longer weaning schedule may be most appropriate for that subgroup of patients, regardless of which sedative infusion they received. While a longer wean may not always be possible depending on the sedative selected, it is an important consideration. Alternate choices are worthy of consideration. For example, clonidine could be used in patients receiving dexmedetomidine or enteral benzodiazepines for patients receiving propofol or midazolam may represent options to provide a longer wean but avoid prolonged duration of mechanical ventilation related to sedative infusions.

Finally, it is possible that we did not capture all potential rebound phenomena by limiting the definition to 24 hours after stopping sedation therapy. This would be particularly relevant with midazolam as it may have accumulated leading to a delay in onset of rebound hypertension. There were 104 propofol patients and 58 midazolam patients in the control group. There was no significant difference between the propofol or midazolam patients with respect to incidence of rebound hypertension in patients who had a history of hypertension. Although it is possible that there were too few patients in the midazolam group to detect a true difference.

Conclusions

When compared to either propofol or midazolam, dexmedetomidine did not increase the

incidence of rebound hypertension upon discontinuation. Hypertension history appears to be associated with an increased risk of rebound hypertension, regardless of which sedative medication is selected. In patients with a history of hypertension, a longer titration of dexmedetomidine may be most appropriate. However, in other patients, less time on sedation may allow for better outcomes as well as lower medication costs.

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