3-1-2019

Long-term beta-blocker therapy safe and effective in reducing cardiomyopathy in patients who actively abuse stimulant drugs

Jessica Bugbee
University of the Pacific, jessica.bugbee1@gmail.com

Long-term beta-blocker therapy safe and effective in reducing cardiomyopathy in patients who actively abuse stimulant drugs.

By

Jessica Bugbee

Capstone Project

Submitted to the Faculty of the

Department of Physician Assistant Education

of University of the Pacific

in partial fulfillment of the requirements

for the degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

March 2019

Introduction:

If anything was learned since Breaking Bad, it's that the devastation due to the methamphetamine problem does not spare a single person. Similarly, cocaine abuse does not have benign effects on the heart. Methamphetamine and cocaine abuse are increasing worldwide including use among the younger population; making recognition of the cardiovascular risks more important than ever.[1,2]

Complaints related to stimulant drug toxicity are common in emergency departments. It has been shown that cocaine is most commonly implicated in drug-related hospitalizations and accounts for 40.3% of drug-related emergency department visits in 2011. Patients who abuse cocaine and methamphetamine are shown to experience frequent cardiovascular complications and are brought to emergency departments more frequently, using larger amounts of hospital resources.[3,4]

Long-term stimulant abuse is known to cause of cardiomyopathy and hypertension. In the United States, heart failure accounts for more than 1 million hospitalizations and $32 billion in costs annually; and stimulant abusers make up over 5% of this population.[1,2,3,4] Patients with reduced ejection-fractions of 10-15% are shown to abuse stimulant drugs and experience frequent heart failure exacerbations placing a great cost on society and healthcare.[5] Beta-blockers are recommended as the most effective agents in systolic heart-failure (HF) that can achieve reverse remodeling but use for prevention of stimulant-induced-cardiomyopathy is not well investigated.[6]

Stimulant created catecholamine excess is the proposed cause of myocardial injury and beta-blockers are currently the only class of medication that can antagonize this. However,

beta-blocker therapy (BBT) has been controversial in this patient population due to reported cases of worsening vasoconstriction during acute toxicity from unopposed alpha-receptor stimulation[3,4,7] and it has been recommended to avoid their use until abstinence from stimulant drugs is confirmed.[1,6]

There is a lack of quality studies investigating the use of long-term BBT in active cocaine users and almost no data investigating this same issue in regard to methamphetamine use.[6] Previous studies have demonstrated coronary vasoconstriction by administering first-generation beta-selective blockers propranolol or esmolol acutely or directly into the coronary arteries of cocaine-positive subjects.[3,4,8] Recent research has suggested that the phenomenon of excessive alpha-receptor stimulation might not be present with nonselective beta-blockers with alpha-blocking properties such as labetalol and newer generation carvedilol.[1,3,4,6]

If long-term BBT can decrease the incidence of stimulant-related cardiovascular complications commonly experienced in methamphetamine and cocaine users, then it may be possible to decrease unnecessary admissions to the hospital and ICU. Therefore, in patients who actively engage in stimulant drug abuse, how does long-term BBT, both selective and nonselective, affect cardiovascular outcomes compared to no BBT regarding prevention of stimulant-induced-cardiomyopathy?

Discussion:

Beta-blocker therapy in acute stimulant toxicity:

Current literature does not recommend the use of beta-blockers in the setting of cocaine-associated-chest-pain (CACP). Small studies and case reports have suggested the use of beta-blockers may exacerbate coronary vasospasm and the toxic effects of cocaine by inducing

unopposed alpha-adrenergic stimulation.[1,3,4] Two high quality systematic clinical reviews have demonstrated lack of evidence preventing the use of selective and nonselective BBT in both acute methamphetamine and cocaine intoxication. Findings show the superiority of beta-blockers in the management of both stimulant-induced hypertension and tachycardia when compared to first-line treatment choices calcium-channel blockers, nitrates and alpha-blockers; which were shown to only attenuate HTN and not tachycardia.[3,4]

The 2012 ACCF/AHA guidelines endorse the use of labetalol in acute stimulant toxicity given certain vital sign parameters and only after a vasodilator is given one hour prior. These guidelines note a lack of literature investigating these effects in methamphetamine users, and currently, recommend that treatment for acute methamphetamine toxicity be the same as for cocaine toxicity pending future investigation.[6]

Current evidence shows that providers have been using BBT despite guidelines during acute stimulant toxicity without causing any adverse cardiac events.[3,4,7,8] A retrospective study examined 376 patients presenting to the emergency department with acute coronary syndrome (ACS) and self-reported cocaine use within 24-hours in the presence of a positive urine drug screen (UDS) for cocaine. Beta-blockers given were metoprolol (45%), carvedilol (26%), labetalol (27%), or atenolol (2%). No differences were found between selective, nonselective beta-blockers, the rate of death, stroke or arrhythmia compared to those not receiving BBT.[7] These findings suggest safety of BBT during the management of patients presenting with ACS secondary to acute cocaine intoxication.

A systematic review and meta-analysis of five studies were performed involving 1,794 patients presenting with CACP. The authors found no increased risk of non-fatal MI or all-cause

mortality in patients given BBT versus none.[8] This evidence supports the safety of BBT in concurrent stimulant toxicity and this same idea can be applied to the use of BBT long-term. If safety can be demonstrated during acute toxicity, then safety is suggested in patients taking daily beta-blockers who also abuse cocaine or methamphetamine.

Beta-blocker therapy following hospital discharge:

Safety has also been demonstrated in patients discharged on BBT immediately following hospitalization for CACP. Both selective and nonselective BBT after hospital discharge shows a 70% reduction in the rate of death over a median follow-up of 972 days compared to no BBT. The authors of this same study admit that patients with CACP have been shown to exhibit a high mortality rate, and outpatient BBT may help protect against cardiovascular death.[9]

A prospective single-center study examined outcomes in 57 patients ≤50 years of age admitted with ACS and urine drug screen (UDS) positive for cocaine. Patients discharged on BBT showed a 12.5% increase in 90-day survival. Discharge on BBT also had 14.7% less chance of death and 2.6% less chance of hospital admission secondary to MI compared to discharge without.[2] The authors of this study support the use of long-term BBT in this patient population.

A retrospective cohort study examined 60 patients with positive UDS for cocaine. Of these patients, 40 (66%) received selective beta-blockers (propranolol, metoprolol, atenolol), 13 patients (21%) received nonselective beta-blockers (carvedilol, labetalol), and 8 patients (13%) received both. Results showed proportionately fewer cases of death and myocardial infarction (MI) during hospital admission and during 5-year follow-up in patients that received BBT (6.1%) compared to none (25.9%).[10] Discharge on BBT after ACS has shown improvement in clinical outcomes in non-stimulant users.[6,9] Evidence also suggests safety of discharge on BBT

after cocaine-related ACS by demonstrating a decreased rate of death and cardiac-related complications during the period following hospital discharge.

Long-term beta-blocker therapy in active methamphetamine use:

Beta-blockers use related to prevention of methamphetamine-induced cardiomyopathy has been minimally investigated.[3,6] Researchers performed a single study based out of two medical centers in Germany in order to describe clinical characteristics and histological changes in the myocardium of 24 subjects with methamphetamine-associated-cardiomyopathy (MACM). Of patients receiving BBT, 20 patients stopped using methamphetamine while four patients continued methamphetamine abuse.[5]

Mean age was 30 years of age and echocardiograms showed severe systolic dysfunction and left ventricular chamber dilatation. The majority had regurgitant valve lesions, ventricular thrombi, and pleural or pericardial effusions. All patients were treated with standard heart failure therapy including the use of BBT. The follow-up period averaged 12-months and improvement in symptoms and ventricular function was only identified in the patients who discontinued methamphetamine abuse.[5]

No benefit of long-term BBT was identified during ongoing methamphetamine use, however, the study only involved four patients using BBT yielding results of low statistical value. Further limitations of this study include an inability to confirm outpatient adherence to BBT therapy and that methamphetamines were not the sole drugs of abuse. Most patients profiled used other substances such as alcohol, heroin, and cocaine which are all known to have cardiotoxic effects. Since most methamphetamine users often simultaneously abuse alcohol

and other drugs[5] it's difficult to say whether or not BBT could counteract the cardiotoxic effects of multiple substances used simultaneously.

This study suggests that only cessation of methamphetamine abuse is associated with improvement in cardiac function and symptoms; whereas continued methamphetamine abuse leads to ongoing heart failure and worse outcome despite concurrent long-term BBT. Given the limitations mentioned previously, future high-quality studies are needed to investigate these findings further.

Long-term beta-blocker therapy in active cocaine use:

The use of long-term BBT in the prevention of cocaine-induced-cardiomyopathy has been investigated on a larger scale. A meta-analysis studied outcomes of BBT among 90-systolic heart failure patients who actively abuse cocaine compared to 177 patients with non-ischemic systolic HF without cocaine use. The authors found no differences in heart failure (HF) readmissions, major adverse cardiovascular events or death when comparing the two groups over a 4,000-day interval. Within HF patients with active cocaine use, mortality rates were not different between nonselective versus selective BBT.[11]

Long-term BBT produces the same outcomes in systolic HF patients despite cocaine abuse, and the authors of this study suggest that this population should not be precluded from its benefits. Limitations of this study include a sample size of mostly males and significant differences between cocaine-positive and cocaine-negative groups regarding BMI, co-morbidities, age and ACE-I use. Another limitation is that this study does not include outcomes of cocaine use without BBT.[11]

A single-center retrospective cohort study decided to investigate outcomes comparing BBT to no BBT in active cocaine users. The study investigated 268 adult systolic HF patients who tested positive for cocaine on UDS. Of the patients involved, 86% were placed on long-term BBT while 14% were not. Results show that 30-day readmission rates related to either all-cause or HF were 21% less with BBT compared to none. No differences were found between these same groups after 1-year.[12]

Limitations of this study include the larger number of patients placed on long-term BBT compared to not which lowers the statistical significance of the findings. Another limitation involves large variation in intervals of follow-up echocardiograms. The authors were unable to evaluate the effects of BBT on left ventricular ejection fraction (LVEF) due to poor patient follow-up and instead resorted to measuring the incidence of all-cause mortality.[12] The authors' inability to assess LVEF in this study is unfortunate since the use of BBT in this population is meant to reduce the instance of cardiomyopathy.

A case-series involving four patients investigated outcomes of long-term BBT by measuring changes in the instance of cardiomyopathy. Results found clinical and echocardiographic (ECHO) recovery with carvedilol therapy in severe systolic HF with ongoing cocaine abuse. None of the patients were prescribed beta-blockers on admission, after 2.5 months each patient was being treated with carvedilol 25 mg twice daily. At mean follow up of 9.25 months, New York Heart Association functional class (NYHA) on average improved by 1.5 and left ventricular ejection fraction (LVEF) improved by 36.5% at follow-up.[13]

None of the patients required hospitalization 1-year after enrollment. Furthermore, each patient had almost full recovery of LVEF during ongoing treatment with carvedilol and

concurrent cocaine abuse during a two-year follow-up. The authors concluded that patients with severe cocaine-induced-cardiomyopathy are capable of achieving full clinical and echocardiographic recovery with a maximum dose of carvedilol.[13] Limitations of this study include the case-series study design and lack of comparison of outcomes without BBT use. Unfortunately, this limits the significance of the study's findings. Strengths include actual measurement of LVEF to determine the success of long-term BBT. Findings from this study are promising and prompt need for future research.

A retrospective analysis was performed on 72 beta-blocker-naive active cocaine users with an ejection fraction <40%. After 12-months, 38 patients receiving BBT were more likely to have an improvement in their NYHA class and LVEF. Results also found lower rates of cardiovascular events and HF hospitalizations compared to 34 patients not receiving BBT. When comparing 23 patients receiving carvedilol against 15 patients receiving metoprolol succinate no difference was found in LVEF improvement while NYHA class showed larger improvement with carvedilol. The majority of patients in the study were able to achieve full or almost full recovery of their LVEF after one year of long-term BBT.[1] This study supports the success of long-term therapy with both selective and nonselective beta-blockers in regard to reducing cardiomyopathy in active cocaine users compared to no BBT.

Limitations include the fact that coronary angiography was performed in only 72% of the patients which lowers the significance of the findings. Also, a cardiovascular magnetic resonance was not performed to investigate the extent of myocardial fibrosis and edema.[1] Therefore, future studies involving coronary imaging are needed to explore the findings of this study further.

Strengths:

Common strengths of the previously mentioned studies include the fact that patients given BBT were reported to be at higher risk for cardiovascular events compared to those not given BBT.[1,2,7,8,9,10] Patients were older, had higher presenting systolic BPs, and more often had a history of hypertension. Those who received BBT in the emergency department showed a statistically larger decrease in systolic blood pressure compared to those receiving BBT in the hospital ward only.[9] Patients also had increased risk of systolic dysfunction compared to patients not given BBT.[7,8,9,10]

Limitations:

Common limitations of the studies used include retrospective cohort study design[1,2,7,9,10,12] and the inclusion of a case series.[13] There was an inability to determine the timing of cocaine ingestion with use of UDS since cocaine can be present in urine 48-72 hours after last ingestion.[2,7,8,9,10] Even though a common limitation between the studies involves the use of UDS to determine illicit drug toxicity, most emergency departments determine cocaine and other illicit drug ingestion through utilization of UDS. Similarly, lack of data regarding cocaine serum levels and knowledge on time of cocaine ingestion could be problematic. Acute cocaine toxicity may have different effects compared to cocaine toxicity determined by positive UDS.[10]

Further limitations include several studies failed to provide data on selectivity, route, and type of BBT used.[2,5,8,12] Authors were unable to assess interim behaviors and treatments after discharge and relied only on data obtained from the index hospitalization and the National Death Index to determine long-term mortality.[9] Also, there was a lack of quantitative data

measuring the frequency of cocaine use[1,5,9,11,12,13] including compliance with BBT during follow up.[1,2,5,9,11,12]

Summary:

BBT has shown to improve cardiovascular outcomes in patients who abuse stimulant drugs. Fear of BBT initiated after evidence proposed that beta-blockers given during acute stimulant toxicity may create an unopposed alpha-receptor stimulation leading to worse outcomes. Current literature shows a lack of evidence that BBT increases coronary vasoconstriction during acute cocaine and methamphetamine toxicity. These same findings demonstrate the superiority of beta-blockers in the management of both stimulant-induced HTN and tachycardia compared to first-line treatment choices calcium-channel blockers, nitrates and alpha-blockers which only attenuate HTN.[1,2,3,4]

There is lack of evidence showing an increase in adverse events when patients are given selective or nonselective beta-blockers for the treatment of tachycardia and hypertension when presenting to the emergency department with ACS or chest-pain following recent cocaine use.[3,4,7,8] Safety has also been demonstrated in patients discharged on selective or nonselective BBT immediately following hospitalization for cocaine-related ACS or chest-pain. These findings show a significant decrease in the rate of death, MI and hospital readmission compared to no BBT during the time period following hospital discharge.[2,9,10]

Regarding long-term BBT in methamphetamine users, evidence from a single study shows that only the cessation of methamphetamine use is associated with improvement in cardiac function and symptoms. Continued methamphetamine abuse leads to ongoing heart failure and worse outcome despite simultaneous long-term BBT.[5] Future high-quality studies

involving methamphetamine users are needed given the limitations and lack of previous literature investigating this topic.

Long-term therapy in cocaine users and non-users demonstrates that selective and nonselective beta-blockers produce the same outcomes in systolic HF patients.[11] Evidence also shows systolic HF patients who use cocaine and are prescribed long-term BBT have a significant decrease in all-cause or HF readmissions within 30 days but no differences in mortality after one year.[12] This study initially aimed to measure LVEF instead of mortality in these patients after one year but was not able due to poor patient follow-up.

In relation to cardiomyopathy outcomes, authors of a four patient case-series found that patients with severe cocaine-induced-cardiomyopathy are capable of achieving full clinical and echocardiographic recovery with the maximum dose of carvedilol.[13] BBT with metoprolol and carvedilol over a 12-month interval has also shown dramatic improvement in NYHA class, LVEF and decrease in cardiovascular events and HF hospitalizations in cocaine users with ejection fractions <40%.[1] Findings support the use of selective and nonselective long-term BBT in the prevention of cardiomyopathy in active cocaine users compared to no BBT.

Conclusion

In conclusion, the use of either selective or nonselective beta-blockers to treat the acute effects of cocaine or methamphetamine toxicity demonstrate safety and efficacy. Avoidance of using BBT in this population is secondary to the fear of causing adverse cardiac events during acute toxicity. Since safety has been demonstrated in recent literature then the use of long-term BBT in patients that regularly use stimulant drugs should demonstrate safety as well. Long-term BBT either selective or nonselective shows success in the prevention of

cardiomyopathy in cocaine users by demonstrating a lower rate of death, MI, hospital readmission and improvement of LVEF and NYHA functional class compared to no BBT use. Therefore, both selective and nonselective long-term BBT prevents the progression of cardiomyopathy in active cocaine users but not methamphetamine. Since a single study has attempted to investigate this topic in methamphetamine users additional studies are needed to determine if long-term BBT can decrease the instance of cardiomyopathy in this population as well.

Long-term BBT is shown to decrease the extent and progression of cocaine-induced cardiomyopathy which may offer patients a greater chance of regaining cardiac function if they one day decide to quit stimulant abuse. Furthermore, improvement in cardiac function and lessening of symptoms has shown to decrease heart failure-related hospital admissions which could decrease the current financial burden placed on healthcare.

Reference/Citation List

1. Lopez, P. D., Akinlonu, A., Mene-Afejuku, T. O., Dumancas, C., Saeed, M., Cativo, E. H., ... & Pekler, G. (2019). Clinical outcomes of B-blocker therapy in cocaine-associated heart failure. International journal of cardiology, 277, 153-158.

2. Cediel, G., Carrillo, X., García-García, C., Rueda, F., Oliveras, T., Labata, C., ... & Bayés-Genís, A. (2018). β-Blocker treatment and prognosis in acute coronary syndrome associated with cocaine consumption: The RUTI-Cocaine Study. International journal of cardiology, 260, 7-10.

3. Richards, J. R., Albertson, T. E., Derlet, R. W., Lange, R. A., Olson, K. R., & Horowitz, B. Z. (2015). Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. Drug and alcohol dependence, 150, 1-13.

4. Richards, J. R., Garber, D., Laurin, E. G., Albertson, T. E., Derlet, R. W., Amsterdam, E. A., ... & Lange, R. A. (2016). Treatment of cocaine cardiovascular toxicity: a systematic review. Clinical Toxicology, 54(5), 345-364.

5. Schürer, S., Klingel, K., Sandri, M., Majunke, N., Besler, C., Kandolf, R., ... & Linke, A. (2017). Clinical characteristics, histopathological features, and clinical outcome of methamphetamine-associated cardiomyopathy. JACC: Heart Failure, 5(6), 435-445.

6. Anderson, J. L., Adams, C. D., Antman, E. M., Bridges, C. R., Califf, R. M., Casey, D. E., ... & Lincoff, A. M. (2013). 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology, 61(23), e179-e347.

7. Fanari, Z., Kennedy, K. K., Lim, M. J., Laddu, A. A., & Stolker, J. M. (2014). Comparison of In-Hospital Outcomes for Beta-Blocker Use Versus Non–Beta Blocker Use in Patients Presenting With Cocaine-Associated Chest Pain. The American journal of cardiology, 113(11), 1802-1806.

8. Pham, D., Addison, D., Kayani, W., Misra, A., Jneid, H., Resar, J., ... & Alam, M. (2018). Outcomes of beta-blocker use in cocaine-associated chest pain: a meta-analysis. Emerg Med J, emermed-2017.

9. Rangel, C., Shu, R. G., Lazar, L. D., Vittinghoff, E., Hsue, P. Y., & Marcus, G. M. (2010). β-Blockers for chest pain associated with recent cocaine use. Archives of internal medicine, 170(10), 874-879.

10. Dattilo, P. B., Hailpern, S. M., Fearon, K., Sohal, D., & Nordin, C. (2008). B-blockers are associated with reduced risk of myocardial infarction after cocaine use. Annals of emergency medicine, 51(2), 117-125.

11. Nguyen, P., Kamran, H., Nasir, S., Chan, W., Shah, T., Deswal, A., & Bozkurt, B. (2017). Comparison of frequency of cardiovascular events and mortality in patients with heart failure using versus not using cocaine. The American journal of cardiology, 119(12), 2030-2034.

12. Egbuche, O. E., Ekechukwu, I. R., Maduabum, N., Obinwa, U., Ukpaka, K. L., Maihemuti, A., & Onwuanyi, A. (2017). Effect of Beta-Blocker Therapy on Hospital Readmission and Mortality in Heart Failure Patients with Ongoing Cocaine Use. Journal of Cardiac Failure, 23(8), S61.

13. Littmann, L., Narveson, S. Y., Fesel, N. M., & Marconi, S. L. (2013). Beta blocker treatment of heart failure patients with ongoing cocaine use. International journal of cardiology, 168(3), 2919-2920.