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Urine drug screen positive for cocaine and amphetamine is not an adverse risk factor for cardiovascular morbidity or mortality in trauma

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ABSTRACT

Background Urine drug screening (UDS) is a component of trauma workup and of perioperative risk evaluation. Illicit stimulant use has been associated with cardiovascular complications. This study investigates the impact of stimulant use and its interaction with surgery on cardiovascular complications in trauma patients.

Methods Patients were identified from the 2017 National Trauma Data Bank. Univariate and multivariate analyses were used to evaluate the effect of amphetamine and cocaine on mortality, myocardial infarction (MI), and stroke. We evaluated three subsets: all screened patients, those who underwent surgery, and those whose surgery was immediate. Significance was tested with χ^2 test for categorical variables, Student's t-test for continuous variables, and logistic regression for multivariate analysis.

Results 317 688 (32.1%) patients underwent UDS. Multivariate analysis showed protective association between cocaine and mortality OR 0.9 (p=0.028). Cocaine was a non-significant predictor of MI and stroke: OR 0.63 (p=0.065) and 0.91 (p=0.502), respectively. Amphetamine was a non-significant predictor of mortality, MI, and stroke: OR 0.97 (p=0.405), 0.80 (p=0.283), and 1.02 (p=0.857), respectively. On univariate analysis, amphetamine showed a protective association with MI for all screened patients: relative risk (RR) 0.58 (p=0.005), and for surgical patients: RR 0.58 (p=0.019). Amphetamine showed a protective association with mortality for all three subsets: RR 0.83 (p<0.001), 0.78 (p<0.001), and 0.71 (p<0.001), respectively. Cocaine showed a protective association with MI for all screened patients: RR 0.45 (p=0.001), and for surgical patients: RR 0.44 (p=0.005). Cocaine showed a protective association with mortality for all three subsets: RR 0.76 (p<0.001), 0.71 (p<0.001), and 0.63 (p<0.001), respectively.

Discussion UDS positive for cocaine or amphetamine is not an adverse risk factor in trauma, including trauma patients who underwent surgery. The apparent protective effects of illicit drugs warrant further investigation.

Level of evidence Therapeutic/care management, level IV.

INTRODUCTION

Discretionary urine drug screening (UDS) is a common component of a trauma workup. It has been shown to have a prognostic value which can help clinicians allocate resources and monitor patients with the appropriate acuity.[1] UDS is also frequently performed as part of a preoperative evaluation for elective surgery. A positive drug test for stimulants, such as cocaine or methamphetamine, is generally perceived as an adverse perioperative cardiac risk factor resulting in cancellation of the procedure.[2] Stimulant use has been associated with an increased risk of cardiac complications, such as tachycardia, hypertension, arrhythmias and myocardial infarction (MI), due to overstimulation of the sympathetic nervous system, vasoconstriction and dysregulation of sodium/potassium channels in the heart.[3 4] However, there is a lack of information on whether the risk of cardiac complications remains elevated in asymptomatic patients who do not show signs of stimulant toxicity. UDS can remain positive for days after drug use, which presents a challenge in evaluating perioperative risk.[5]

A patient population that routinely undergoes surgery despite having a positive drug screen is that of trauma patients, who often require emergent procedures that cannot be delayed. Trauma patients have a high prevalence of illicit substance use, with an estimated frequency of preinjury substance use of 20% to 50%.[6 7] A recent study done by our group[8] investigated the cardiac risk associated with surgical procedures in patients who had a positive UDS using the National Trauma Data Bank (NTDB). The results showed that a positive drug screen was not associated with increased perioperative cardiac morbidity or mortality, and in fact was a marker of lower risk. The analysis was done using an NTDB data set that only characterizes drug screen results as positive or negative, with no further breakdown into what substance was responsible for the positive test. Therefore, it is possible that the effect of cardioactive drugs was masked by other drugs responsible for the positive screen. Recently, the NTDB has provided more detailed information on the specific class of drug that led to a positive drug screen. Therefore, the goal of this study is to investigate the impact of stimulant use on perioperative mortality and cardiovascular risk in trauma patients. Our hypothesis is that a UDS positive for stimulant drugs is associated with increased cardiovascular risk and mortality in trauma patients, both for the operative and non-operative subsets of the population. The null hypothesis is that there is no association.

METHODS

The NTDB is a registry of trauma data from multiple US trauma centers. The year 2017 was chosen because this is the first year for which specific drugs

Table 1 Baseline characteristics

Characteristics	No amphetamine	Amphetamine	No cocaine	Cocaine
Sex, female	96 986 (33.7%)	8505 (28.8%)	99 385 (33.9%)	6106 (24.6%)
Race (white vs. non-white)	195 290 (67.8%)	22 218 (75.2%)	203 241 (69.4%)	14 267 (57.5%)
Hispanic ethnicity	14 498 (28.5%)	3577 (45.6%)	14 564 (28.1%)	3511 (51.1%)
Angina pectoris	231 (0.1%)	9 (0.0%)	232 (0.1%)	8 (0.0%)
Myocardial infarction	2083 (0.7%)	157 (0.5%)	2115 (0.7%)	125 (0.5%)
Congestive heart failure	7855 (2.7%)	543 (1.8%)	7993 (2.7%)	405 (1.6%)
Hypertension	76 997 (26.7%)	5362 (18.2%)	77 528 (26.5%)	4831 (19.5%)
Diabetes mellitus	30 797 (10.7%)	2038 (6.9%)	30 990 (10.6%)	1845 (7.4%)
Peripheral arterial disease	1035 (0.4%)	67 (0.2%)	1043 (0.4%)	59 (0.2%)
Stroke	5786 (2.0%)	359 (1.9%)	5805 (2.0%)	340 (1.4%)
Chronic renal failure	2787 (1.0%)	120 (0.4%)	2810 (1.0%)	97 (0.4%)
Anticoagulant use	15 212 (5.3%)	848 (2.9%)	15 372 (5.2%)	688 (2.8%)
Bleeding disorder	4178 (1.4%)	135 (0.5%)	4189 (1.4%)	124 (0.5%)
Cirrhosis	3200 (1.1%)	306 (1.0%)	3221 (1.1%)	285 (1.1%)
Emphysema	15 262 (5.3%)	1322 (4.5%)	15 406 (5.3%)	1178 (4.7%)
Dementia	8474 (2.9%)	372 (1.3%)	8612 (2.9%)	234 (0.9%)
Disseminated cancer	1468 (0.5%)	42 (0.1%)	1472 (0.5%)	38 (0.2%)
Receiving chemotherapy	661 (0.2%)	30 (0.1%)	673 (0.2%)	18 (0.1%)
Alcoholism	24 939 (8.7%)	2544 (8.6%)	24 278 (8.3%)	3205 (12.9%)
Smoker	64 866 (22.5%)	11 714 (39.7%)	65 914 (22.5%)	10 666 (43.0%)
History of substance abuse	24 709 (8.6%)	8457 (28.6%)	25 324 (8.6%)	7842 (31.6%)
Positive alcohol	63 808 (29.1%)	6103 (25.4%)	61 045 (27.5%)	8866 (42.0%)
Mechanism (penetrating)	30 478 (10.6%)	5149 (17.4%)	31 119 (10.6%)	4508 (18.2%)
Head injury AIS score >2	56 023 (19.4%)	5181 (17.5%)	56 746 (19.4%)	4458 (18.0%)
Chest injury AIS score >2	45 528 (15.8%)	5449 (18.4%)	46 888 (16.0%)	4089 (16.5%)
Abdominal injury AIS score >2	13 973 (4.8%)	2093 (7.1%)	14 525 (5.0%)	1541 (6.2%)
Extremity injury AIS score >2	41 762 (14.5%)	4806 (16.3%)	43 017 (14.7%)	3551 (14.3%)
Major surgery	106 408 (36.9%)	12 520 (42.4%)	108 701 (37.1%)	10 227 (41.2%)
Immediate major surgery	32 560 (11.3%)	4223 (14.3%)	33 438 (11.4%)	3345 (13.5%)
Age, mean	45.79	41.26	45.72	41.19
BMI, mean	27.2	26.67	27.19	26.76
Total GCS, mean	13.7	13.5	13.7	13.5
Injury Severity Score, mean	10.3	11.1	10.4	10.6

AIS, Abbreviated Injury Scale; BMI, body mass index; GCS, Glasgow Coma Scale.

were reported with the UDS results. At the time of analysis, it was the latest year available.

Surgery is classified as major according to a database of International Classification of Diseases-10th Revision procedure codes provided by the Agency for Healthcare Research and Quality.[9] Major surgery is defined as 'procedures that are considered operating room procedures'. Procedures are classified as immediate based on the emergency department disposition. If a patient is transferred directly from the emergency department to the operating room, the procedure is considered immediate. Cardiac and non-cardiac comorbidities are analyzed as individual categorical variables rather than an index. Patients were classified as positive for amphetamine or cocaine independently of UDS results for other drugs, including patients positive for both amphetamine and cocaine.

Analysis was performed for all drug-tested patients. Baseline characteristics are compared for tested versus non-tested patients, and for patients who are positive versus negative for amphetamine and cocaine. Univariate analysis was performed for all drugs included with the UDS results versus all complications reported in the registry. Further univariate analysis of stimulant drugs was performed for the subsets including all drug-tested patients, those who underwent surgery, and those who underwent immediate emergency surgery. For the stimulant drug analysis, predictor variables were UDS-positive results for methamphetamine and cocaine. Outcome variables were mortality, MI, and stroke. X^2 was used to test for significance for categorical variables.

Multivariate analysis was performed using a multivariate logistic regression with predictor variables of positive amphetamine and cocaine UDS results, age, sex, race, cardiac and non-cardiac comorbidities reported by the NTDB, Injury Severity Score (ISS), mechanism of trauma, trauma regions of head, chest, abdomen, and extremity, surgery, and emergency surgery.

Statistics were performed with the SPSS V.26.0 statistical package (IBM).

RESULTS

There are 997 970 trauma admissions recorded in the NTDB for 2017. A total of 7813 arrived in the emergency room with

Table 2 Univariate analysis of cocaine and amphetamine vs. MI, stroke, and mortality

	No						No					
Outcome	Amp	%	Amp	%	RR	P value	Cocaine	%	Cocaine	%	RR	P value
All patients	288 154	90.70	29 534	9.30			292 868	92.19	24 820	7.81		
MI	**441**	**0.15**	**26**	**0.09**	**0.58**	**0.005**	**450**	**0.15**	**17**	**0.07**	**0.45**	**<0.001**
Stroke	785	0.27	75	0.25	0.93	0.561	803	0.27	57	0.23	0.84	0.195
Mortality	**10 474**	**3.63**	**896**	**3.03**	**0.83**	**<0.001**	10 682	**3.65**	**688**	**2.77**	**0.76**	**<0.001**
All surgical patients	106 408	89.47	12 520	10.53			108 701	91.40	10 227	8.60		
MI	**280**	**0.26**	**19**	**0.15**	**0.58**	**0.019**	**287**	**0.26**	**12**	**0.12**	**0.44**	**0.005**
Stroke	588	0.55	58	0.46	0.84	0.198	601	0.55	45	0.44	0.8	0.138
Mortality	**4464**	**4.2**	**411**	**3.28**	**0.78**	**<0.001**	**4568**	**4.2**	**307**	**3**	**0.71**	**<0.001**
Immediate surgery	32 560	88.52	4223	11.48			33 438	90.91	3345	9.09		
MI	72	0.22	5	0.12	0.54	0.169	74	0.22	3	0.09	0.41	0.112
Stroke	202	0.62	19	0.45	0.73	0.177	203	0.61	18	0.54	0.89	0.623
Mortality	**1886**	**5.79**	**174**	**4.12**	**0.71**	**<0.001**	**1938**	**5.8**	**122**	**3.65**	**0.63**	**<0.001**

Significant protective associations shown in bold.
Amp, amphetamine; MI, myocardial infarction; RR, relative risk.

no signs of life or with signs of life not recorded. These were excluded, leaving 990 157 trauma admissions. A total of 317 688 (32.1%) were tested for drugs. Characteristics of patients who underwent a UDS versus those who did not are presented in online supplemental table 1. Results for the following drugs are recorded: amphetamine, barbiturate, benzodiazepines, cocaine, ecstasy, methadone, opioid, oxycodone, phencyclidine, tricyclic antidepressants, and cannabinoids.

Comparison of baseline characteristics (table 1) shows that users of both methamphetamine and cocaine tend to be younger than non-users. Stimulant drug users have a higher likelihood of being male, having a history of substance abuse, and being a victim of penetrating trauma. In general, rates of chronic disease tend to be lower for stimulant drug users.

Univariate analysis of UDS-positive results for all drugs tested showed a protective association with mortality, except for tricyclic antidepressants and methadone which showed no significant association (online supplemental table 2). Positive UDS results showed varying protective and harmful associations with individual complications. Most had a relative risk close to 1. The drug significantly associated with the greatest number of complications was benzodiazepines, whose only protective association was with mortality.

On univariate analysis cocaine and methamphetamine showed protective association with MI and mortality in all drug-tested patients, and in those who underwent major surgery (table 2). Both drugs also showed protective association with mortality for the group who underwent immediate emergency surgery. There were no harmful associations with cardiovascular complications or mortality for stimulant drugs.

Multivariate analysis (table 3) shows that cocaine has a protective association with mortality. Stimulant drugs have no harmful association with mortality or cardiovascular morbidity. Advancing age, ISS, and various comorbidities show a harmful association with mortality and cardiovascular morbidity. The strongest predictor of cardiovascular morbidity is major surgery.

The addition of blood alcohol level (BAL) to the model did not change the significance of any of the predictor values and had a minimal effect on the ORs. We omitted BAL from the final model because 20.1% of patients screened for drugs were not screened for alcohol, which would result in the omission of many cases.

DISCUSSION

Use of illicit stimulant drugs has been associated with increased morbidity in both the trauma and perioperative setting.[1 10] To help manage this risk, UDS is used to identify drug-positive patients. However, a positive UDS does not always correlate with acute drug intoxication. For instance, the UDS for cocaine measures levels of an inactive metabolite, which can remain in the urine up to a week after use, making it an unreliable indicator of acute intoxication.[11] This makes risk stratification after a positive UDS challenging. Currently, there are no universal guidelines to evaluate a patient's perioperative risk after a positive UDS, but a result positive for stimulant drugs is widely considered a contraindication for elective general anesthesia. A study conducted by Elkassabany *et al* found that two-thirds of the clinicians surveyed would elect to cancel surgery for these patients, even in the absence of any symptoms of acute intoxication.[5] Canceling elective surgery can delay care in a vulnerable patient population, resulting in adverse health outcomes. It can also result in financial losses and waste of resources. It is difficult to measure the effect that illicit substance use has on elective perioperative complications, given the reluctance to operate on this population. Trauma patients, however, regularly undergo emergency procedures despite having a positive drug screen, allowing us to examine the impact of substance use on perioperative complications.

Our analysis showed protective or neutral association of stimulant drugs with cardiovascular morbidity or mortality on the overall population, and on the subset who underwent major surgery. This lack of harmful association also applied to the group of patients who underwent immediate surgery. If the effects of the substances measured on a UDS conferred excess cardiovascular risk, one would expect this population to be especially vulnerable because the substances had less time for excretion or metabolism. However, even for the group requiring immediate surgery, stimulant-positive UDS is not associated with increased cardiovascular morbidity or mortality.

Table 3 Multivariate analysis of stimulant drugs vs. mortality and cardiovascular outcomes

	Multivariate analysis					
	Mortality		MI		Stroke	
Characteristics	OR	P value	OR	P value	OR	P value
Amphetamine	0.966	0.405	0.801	0.283	1.023	0.857
Age	1.026	<0.001	1.052	<0.001	1.017	<0.001
Sex, female	0.805	<0.001	0.677	<0.001	1.132	0.106
Race (white vs. non-white)	0.959	0.107	0.915	0.471	1.163	0.054
Angina pectoris	0.521	0.099	1.022	0.983	0	0.995
Myocardial infarction	1.243	0.035	2.441	<0.001	1.114	0.739
Congestive heart failure	1.804	<0.001	1.544	0.008	0.969	0.866
Hypertension	0.774	<0.001	1.372	0.005	1.325	0.002
Diabetes mellitus	1.036	0.321	1.554	<0.001	1.439	<0.001
Peripheral arterial disease	1.777	<0.001	1.365	0.396	1.51	0.261
Stroke	1.142	0.042	1.225	0.34	2.473	<0.001
Chronic renal failure	1.946	<0.001	1.118	0.7	0.945	0.851
Anticoagulant use	1.209	<0.001	1.673	<0.001	1.365	0.015
Bleeding disorder	1.118	0.138	0.91	0.752	1.601	0.025
Cirrhosis	3.207	<0.001	1.031	0.934	0.847	0.594
Emphysema	1.593	<0.001	1.408	0.016	1.029	0.843
Dementia	1.016	0.788	0.64	0.064	0.599	0.036
Disseminated cancer	2.156	<0.001	0.973	0.953	1.087	0.833
Receiving chemotherapy	1.682	0.001	1.388	0.582	1.783	0.217
Alcoholism	0.991	0.829	1.09	0.611	1.062	0.628
Smoker	0.512	<0.001	1.632	<0.001	0.936	0.478
Chronic substance abuse	0.767	<0.001	0.865	0.487	0.915	0.495
Injury Severity Score	1.127	<0.001	1.039	<0.001	1.048	<0.001
Mechanism (penetrating vs. blunt)	3.853	<0.001	1.113	0.631	1.084	0.545
Head injury AIS score >2	2.987	<0.001	1.221	0.111	2.594	<0.001
Chest injury AIS score >2	0.782	<0.001	1.366	0.011	1.377	<0.001
Abdominal injury AIS score >2	0.633	<0.001	1.575	0.01	1.072	0.551
Extremity injury AIS score >2	0.687	<0.001	1.144	0.263	0.955	0.595
Had major surgery during admission	0.697	<0.001	2.901	<0.001	4.075	<0.001
Had immediate major surgery	1.360	<0.001	1.124	0.41	1.307	0.002
Cocaine	0.902	0.028	0.627	0.065	0.908	0.502
Age	1.026	<0.001	1.052	<0.001	1.017	<0.001
Sex, female	0.804	<0.001	0.675	<0.001	1.13	0.11
Race (white vs. non-white)	0.963	0.144	0.937	0.598	1.166	0.05
Angina pectoris	0.52	0.098	1.015	0.988	0	0.995
Myocardial infarction	1.243	0.035	2.434	<0.001	1.114	0.74
Congestive heart failure	1.804	<0.001	1.544	0.008	0.968	0.864
Hypertension	0.774	<0.001	1.375	0.005	1.324	0.002
Diabetes mellitus	1.035	0.327	1.554	<0.001	1.439	<0.001
Peripheral arterial disease	1.777	<0.001	1.364	0.398	1.509	0.262
Stroke	1.142	0.041	1.229	0.332	2.473	<0.001
Chronic renal failure	1.942	<0.001	1.113	0.713	0.944	0.847
Anticoagulant use	1.209	<0.001	1.675	<0.001	1.364	0.015
Bleeding disorder	1.116	0.144	0.908	0.744	1.596	0.026
Cirrhosis	3.21	<0.001	1.031	0.934	0.847	0.594
Emphysema	1.594	<0.001	1.409	0.016	1.029	0.843
Dementia	1.015	0.801	0.639	0.064	0.598	0.036
Disseminated cancer	2.154	<0.001	0.974	0.954	1.085	0.836
Receiving chemotherapy	1.68	0.002	1.381	0.588	1.779	0.219
Alcoholism	0.992	0.847	1.095	0.593	1.061	0.633
Smoker	0.513	<0.001	1.644	<0.001	0.94	0.508
Chronic substance abuse	0.773	<0.001	0.892	0.583	0.933	0.595

Continued

Table 3 Continued

	Multivariate analysis					
	Mortality		MI		Stroke	
Characteristics	OR	P value	OR	P value	OR	P value
Injury Severity Score	1.127	<0.001	1.039	<0.001	1.048	<0.001
Mechanism (penetrating vs. blunt)	3.86	<0.001	1.123	0.603	1.088	0.526
Head injury AIS score >2	2.988	<0.001	1.219	0.115	2.593	<0.001
Chest injury AIS score >2	0.782	<0.001	1.364	0.012	1.377	<0.001
Abdominal injury AIS score >2	0.632	<0.001	1.572	0.011	1.072	0.549
Extremity injury AIS score >2	0.687	<0.001	1.142	0.269	0.955	0.599
Had major surgery during admission	0.698	<0.001	2.902	<0.001	4.077	<0.001
Had immediate major surgery	1.359	<0.001	1.121	0.423	1.306	0.002

AIS, Abbreviated Injury Scale; MI, myocardial infarction.

While these findings are consistent with our previous study,[8] they still seem counterintuitive given the evidence of cardiotoxicity with stimulant use.[3 4] The protective effects observed with stimulant use may be a result of unknown confounding variables; however, it is also possible that these protective effects are based on a true pharmacologic effect. Evidence of protective effects with stimulant use in trauma patients has been observed in previous studies. Ryb and Cooper showed that patients who had a positive UDS for cocaine had decreased rates of cardiovascular complications when undergoing surgery during the first day of admission[12] and Cheng *et al* showed amphetamine use to be associated with lower rates of mortality.[1] There are also studies that show no significant difference in mortality or cardiovascular complications in trauma patients who test positive for stimulants.[13–16] This is further validated by recent studies examining the incidence of hemodynamic events under anesthesia to be similar between patients who screen positive for stimulants and patients who have a negative UDS, with the rates of vasopressor use during surgery similar between both groups.[17–19]

It can be difficult to separate the effects of acute and chronic stimulant use. While we do not know the duration of substance use for each patient, 28.6% and 31.6% of the amphetamine and cocaine group, respectively, in our population had a documented history of chronic substance use. Chronic substance abuse could potentially have a harmful or protective effect. On one hand, chronic stimulant use can result in dilated cardiomyopathy and an increased risk of acute coronary syndrome.[3 4] However, an alternative hypothesis is that chronic users of methamphetamine and cocaine may have undergone a selection process that leaves survivors less vulnerable to catecholamine-induced cardiovascular stress. Having already survived a stimulant stressor, this population may be relatively resistant to further cardiovascular compromise. Most of our UDS-positive patients did not have a diagnosis of chronic substance abuse. Since we do not know the timing of substance use based on a positive UDS, it is possible that, in spite of positive results, many of our patients were not suffering from acute or chronic effects of illicit drugs at the time of the trauma and subsequent treatment.

While our study findings do not show an association of stimulant use with increased risk of MI, stroke, and mortality, both stimulants are associated with increased rates of surgical site infections, sepsis, and ventilator-associated pneumonia. Stimulants can cause vasoconstriction, resulting in poor wound healing and more susceptibility to surgical site infections. In addition, chronic stimulant abuse can result in malnutrition which can further increase a patient's susceptibility to infections.[20] Other studies have shown that cocaine can negatively impact the functioning of immune cells and mediators.[20 21]

Strengths of study

We used a large multicenter database for greater statistical power. We were able to show associations between the use of individual drugs and a wide variety of complications. Our study further investigated the use of stimulant drugs and the interaction with surgical procedures to help assess the influence on perioperative risk.

Limitations of study

Not all patients were evaluated for drug use because facilities did not have standardized criteria for choosing which patients to screen. Inconsistent selection of patients for UDS could potentially introduce bias. The UDS does not provide data about the level of the substance present or the time that the substance was used, thus UDS-positive patients may not have been acutely intoxicated. Our analysis shows lower rates of surgical interventions in positive amphetamine/cocaine groups. It is possible that some higher risk patients were excluded from surgery based on UDS results, which could mask a harmful effect. Terms were included in the multivariate analysis to adjust for surgical treatment, but this could still represent a subtle bias. The multivariate analysis adjusts for baseline imbalance; however, the retrospective nature of the study introduces the possibility of unknown and unmeasured confounding variables, thus it cannot establish cause and effect.

CONCLUSION

Our study showed that a UDS positive for cocaine or methamphetamine is not an adverse risk factor for death, stroke, or MI in trauma. This was true for the overall trauma population as well as for the patients who underwent surgery.

This lack of harmful association calls into question the perceived perioperative risk of these drugs and the policy of canceling surgery based on a positive UDS. The results of UDS for illicit drugs show a variety of harmful and protective associations with mortality and complications in trauma patients. It is likely to represent a complex interaction of patient selection and pharmacologic effects. In the setting of a positive UDS, evaluation for signs of acute intoxication, cardiovascular compromise and hemodynamic instability should help guide evaluation of cardiovascular risk and the timing of surgery.

Contributors SS and JC gathered, analyzed and interpreted the patient data regarding the treatment groups and outcomes. CF participated in analyzing the data and interpreting its clinical significance. All authors read and approved the final article.

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