Study Protocol

Intensive blood pressure control in patients with acute type B aortic dissection (RAID): study protocol for randomized controlled trial

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Background: Blood pressure control is an essential therapy for patients with acute type B aortic dissection (ABAD) and should be maintained throughout the entire treatment. Thus, vast majority current guidelines recommend control the blood pressure to lower than 140/90 mmHg. Theoretically, a much lower target may further decrease the risk of propagation of dissection. However, some argued that too lower blood pressure would compromise the organ perfusion. Thus, there is no unanimous optimal target for blood pressure in patients with ABAD so far. The present study aimed to investigate the optimal blood pressure target for patients with ABAD, in the hope that the result would optimize the treatment of aortic dissection (AD).

Methods: The study is a multi-center randomized controlled clinical trial. Study population will include patients with new diagnosed ABAD and hypertension. Blocked randomization was performed where intensive blood pressure control (<120 mmHg) with conventional blood pressure control (<140 mmHg) were allocated at random in a ratio of 1:1 in blocks of sizes 4, 6, 8, and 10 to 360 subjects. Interim analysis will be performed. The primary outcome is a composite in-hospital adverse outcome, including death, permanent paraplegia or semi- paralysis during the hospitalization, and renal failure requiring hemodialysis at discharge. While the secondary outcomes include the aortic size, lower extremity or visceral ischemia, retrograde propagation into aortic arch or ascending aorta, mortality in 6 months and 1 year, intensive care unit (ICU) length of stay, total length of hospital stay, creatinine level, and surgical or endovascular intervention.

Ethics and dissemination: The study was approved by the institutional review board of Sir Run Run Shaw Hospital (approval number: 20160920-9). Informed consent will be obtained from participants or their next-of-kin. The results will be published in a peer-reviewed journal and shared with the worldwide medical community.

Trial registration: NCT03001739 (https://register.clinicaltrials.gov/).

Keywords: Aortic dissection (AD); Stanford B type; intensive care unit (ICU); mortality; randomized controlled trial

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Introduction

Aortic dissection (AD) aneurysm is a common catastrophic aortic disease in clinical setting. In the U.S., the prevalence is approximate 2.9–3.5 cases/100,000 persons per year (1), while recent evidence showing an increasing incidence of up to 14 cases per 100,000 patients per year. AD aneurysm can be classified into the types of Stanford A and B based on whether the ascending aorta was being involved. Stanford A type AD generally requires emergency surgery. The mortality in the first 24 hours can reach to 33% if appropriate managements were delayed or not timely started. Moreover, the mortality will rise to 50% in 48 hours if the patient was not rational managed. That is, the mortality for Stanford A type AD rises at a rate of 1% for each hour (2). Nevertheless, as for acute type B aortic dissection (ABAD), which is generally accounted for one thirds of all AD and is especially more common among Chinese due to the suboptimal control of blood pressure. Optimal treatment of ABAD from symptom onset remains uncertain. Conservative therapy of heart rate and blood pressure control in the acute phase is the essential treatment for patient without serious complications such as concurrent mesenteric artery or lower limb arterial embolism. The long-term survival of ABAD is still low though great improved in medication optimization and surgical repair technique in the past decades. It was reported that 5- and 10-year survival rates for ABAD were 60% and 35% respectively (3). As the development of minimally invasive techniques in recent years, the endovascular repair procedure has become a routine procedure in the treatment of patient with ABAD, this rendered an improved prognosis with a 5-year survival rate close to 80% (4).

Hypertension is well known as the most common cause for AD. The statistics from International Registry of Acute Aortic Dissection (IRAD) demonstrated that 72.1% of AD patients had a history of hypertension (5). The hypertension may aggravate hematoma expansion and results in serious consequences. Therefore, effectively blood pressure control may alleviate the severe pain caused by acute AD and lessen the progression of arterial dissection. The control of hypertension is the primary treatment for acute AD, and should be maintained throughout the entire treatment. Currently, all guidelines recommended to decline the transaortic pressure via controlling the heart rate and blood pressure for AD patient in acute phase (2,6). Theoretically, to control the blood pressure to the minimal level meeting the sufficient end-organ perfusion can decrease the risk of vessel rupture as much as possible. Whereas, too much low blood pressure target may increase the mortality of patients. Powell and his colleague found when the minimum blood pressure increased by 10 mmHg (*vs.* <70 mmHg, maximal to 120 mmHg) for patients with ruptured abdominal aortic aneurysm, the risk of death decreased by 12% (OR =0.88, P<0.001) (7).

Nevertheless, there is no unanimous optimal target for blood pressure in patients with AD so far. The American Heart Association and the Canadian Cardiovascular Society recommend the blood pressure should be controlled to lower than 140/90 mmHg, while for patients with diabetes or chronic renal failure, the blood pressure target should be no less than 130/80 mmHg (2,6). Recently, the Japanese Circulation Society recommended that the blood pressure should be controlled to no less than 130 mmHg (8). However, few large-scale, randomized, controlled studies were reported on the effect of different blood pressure control levels on the prognosis of patients with AD. We hypothesized that the intensive control of blood pressure to <120 mmHg, compared to <140 mmHg, may improve the patients' outcome. Thus, in this study, we planned to compare the effect of intensive blood pressure control (<120 mmHg) with conventional blood pressure control (<140 mmHg) on the prognosis of ABAD patients, and to identify the therapeutic efficacy of intensive blood pressure control on the ABAD patients.

Methods

Study design and setting

The study was a prospective randomized controlled trial that will recruit a maximal of 360 patients in eight

tertiary Chinese hospitals over 2 years. All patients with new diagnosed ABAD in the participating hospitals will be screened for potential eligibility. The study was approved by the ethics committee of the hospitals (20160920-9). Written informed consents will be signed by the patients or their legally authorized representatives. The study was registered in the website of ClinicalTrial.gov (registration no. NCT03001739).

Sites and patients

A total of eight hospitals attended the kick-off meeting held in Courtyard Marriott, Hangzhou, March 19th, 2016, and discussed the research protocol and details. The amended research protocol was passed according to revised discussion results and the agreement of all participating units. The method and apparatus used for blood pressure measurement were unified. For every patient, obtain a minimum of two blood-pressure measurements at intervals of at least 1 minute. Record the average of the measurements as the blood pressure. The process of blood pressure measurement is as previous described. First, correctly positioning the patient and bared the arm to the shoulder. Then, cuff was placed on the bare arm, approximately 2 cm above the elbow crease and directly over the brachial artery. After that, the stethoscope was placed over the brachial artery, then using sufficient pressure for the cuff and the systolic and diastolic blood pressure were recorded correspondingly. Given branch occlusion may happen for some patients, all the extremities were taken to avoid underestimate the blood pressure. All hospitals will adopt similar non-invasive blood pressure monitoring method and unified monitoring frequency to observe whether the blood pressure is controlled within the target range in two groups. Likewise, the blood pressure target after discharge was maintained at the same levels.

All patients with AD from the participating hospitals who conform to the following inclusion and exclusion criteria will be randomized. Inclusion criteria: newly diagnosed patients with Stanford type B acute AD and systolic blood pressure >160 mmHg. Patients with following conditions will be excluded:

(I) Age <18 years,
(II) In pregnancy,
(III) Diagnosis of AD was made 48 hours or more prior,
(IV) Dissection due to aortic intramural hematoma or penetrating atherosclerotic ulcer,
(V) With history of previous surgical or interventional endovascular treatment for aortic diseases,
(VI) With traumatic aortic injury,
(VII) With history of cerebrovascular accident, brain surgery, chronic renal insufficiency, and mesenteric vascular thrombosis or dissection,
(VIII) AD patient concomitant with new cerebral infarction, or ischemic mesenteric artery or lower limb arteries which requiring urgent surgical interventions,
(IX) With obvious contraindications for antihypertensive therapy, such as severe carotid stenosis, cerebral infarction in acute phase,
(X) Pathogenesis of the dissection was due to congenital aortic hypoplasia, such as Marfan syndrome, connective tissue diseases.

Randomization

Blocked randomization was adopted and the intensive and conventional blood pressure control treatments were allocated at random in a ratio of 1:1 in blocks of sizes of 4, 6, 8, and 10 to 360 subjects. The study is an open label trial. After investigators in each participating centers screened the potential patients within 4 hours after acute onset, they will get a number from a pre-allocated envelope and which denotes which group the patient will be allocated to.

Treatments

All the patients were admitted to intensive care unit (ICU) or general wards at the discretion of doctors. Based on the guidelines of aortic management, all patients received analgesic therapy and standard control of heart rate and blood pressure treatments. Intravenous esmolol was used for continuous control of heart rates. Choice of intravenous antihypertensive agents was at the discretion of the in charge physicians. After the stabilization of the situation, the intravenous medications were shifted to the oral treatments. The target blood pressure for the intensive and conventional groups were <140 and <120 mmHg respectively. An acceptable mean arterial pressure was 65 mmHg. For most patients, they may undergo an endovascular treatment approximate two weeks later.

Study endpoints

The primary outcome is a composite in-hospital adverse outcome, including death, permanent paraplegia or semi-paralysis during the hospitalization, and renal failure

requiring hemodialysis at discharge (9).

The secondary outcomes include the aortic size, lower extremity or visceral ischemia, retrograde propagation into aortic arch or ascending aorta, mortality in 6-month and 1-year, ICU length of stay, total length of hospital stay, creatinine level and surgical or endovascular intervention.

Data collection

Research coordinators of individual participating hospital will collect the required data on the case report form. However, the data was de-named and special security code was required to access the data. To facilitate the communications between investigators, the case report form was written in Chinese. The primary research institute is responsible for collecting and checking the data of all centers; and will contact the co-investigators in various centers for checking or revising should they had any question. The primary research institute has established an independent study quality control group to implement the disposal plan for all unexpected circumstances that may occur.

Sample size calculation and interim analysis

The primary outcome was a composite in-hospital adverse outcome, including the death, stroke, permanent paraplegia or semi- paralysis during the hospitalization, and renal failure requiring hemodialysis at discharge. Bashir *et al.* (9) reported that the incidence of comprehensive nosocomial severe prognostic adverse events of ABAD was 45.2%. Assume that the incidence of severe prognosis adverse event in comprehensive hospital after intensive blood pressure control could be reduced to 30% (10), so a total of 322 subjects enrolled in the study are sufficient to find the difference statistically between two groups through the appropriate software calculation under the power of 0.8 and at the two-side test with α=0.05. Considering a dropout rate of 10%, it is proposed to include 360 cases totally into the study. A formal interim analysis was conducted halfway during study enrollment. The overall type I error was controlled using an O'Brien-Fleming spending function, with a final significance level of 0.05 for the primary end point.

Statistical analysis

Descriptive data were reported as either mean ± SD, median (interquartile range) or number and percentage. With respect to the differences between two groups, categorical variables were compared using chi-square analysis. Continuous variables were compared using Independent Sample *t* test for normally distributed data and Mann-Whitney *U* test for non-normally distributed data. For survival analyses, we generated Kaplan-Meier estimates, assessed between-group differences using the log-rank test, and expressed the data as cumulative mortality curves. Statistical analysis was performed by using SPSS 16.0 (Chicago, Ill, USA) and PASS 11.0. Statistical significance was defined as a P value <0.05.

Discussion

ABAD comprises approximately 30% of all AD cases. In contrast with type A AD, patients with type B dissection are tend to be older, have higher rates of atherosclerosis. Initial goals for acute AD management are directed at control of blood pressure and heart rate, which subsequently limiting propagation of the false lumen by controlling aortic shear stress. Whilst medical management has demonstrated an in-hospital mortality rate less than 10%, acute type B aortic disease continues to evolve eventually resulting in complicated type B disease. Moreover, complicated ABAD shows even more striking mortality as high as 30%, particularly in the elderly (11,12). Poor control of blood pressure was believed to be one of the main reasons for the progress of the type B AD into complications or even the laceration extended to the ascending aorta. Delsart and colleague demonstrated that a systolic blood pressure more than 130 mmHg was associated with a bigger aortic enlargement in type B AD (P=0.02) (13). In another study of 25 years follow-up in 252 patients who received repair of acute type A AD, patients who maintained a systolic blood pressure <120 mmHg had improved freedom from reoperation, compared to those target blood pressure 120–140 or >140 mmHg (14). Hence, most guidelines recommended a reasonable initial target for systolic blood pressure is between 100 and 120 mmHg (2,6). However, this target is based on the hypothesis that all the end-organs blood supply is not compromised. Data from IRAD has shown that approximately one quarter of patients presenting with ABAD are followed into complicated category, including malperfusion of spinal arteries leading to paresis, and paraplegia or malperfusion of visceral arteries leading to abdominal pain (15). Thus, how to balance the decrease of blood pressure to the lowest amount and maintain adequate end-organ perfusion is a challenge. Given vast majority patients with type B AD had a history of hypertension,

a too lower target of blood pressure may comprise the cerebral perfusion or complicated organ perfusion, which consequently caused stroke or other morbidity such as ischemic intestinal necrosis. On the other hand, a much strict blood pressure target and sometimes constrain on the patients daily activities may aggravate patients' worry, which inversely increased the blood pressure. Unfortunately, there is no empirical data or trials to guide the optimal blood pressure target setting for various patients. Hence, the study was designed to bridge the gap.

There were some limitations of our study. First, this was an open label study, physicians in the local hospitals knew exactly the patients' blood pressure target. However, we did not think this will affect the reliability of the result because all the data would be collect by coordinators blinded to the allocation of groups. Second, we could not just assess the pure effect of medical therapy on the patients' outcome because most of the patients will undergo an endovascular repair nowadays. Nevertheless, given the randomized trial nature, the possibility of the patient to undergo an endovascular repair was equal between groups.

In conclusion, we believe that the study will provide new insight into the of blood pressure management of patients of ABAD and subsequently improve the outcomes.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the ethics committee of the hospitals (20160920-9). Written informed consents will be signed by the patients or their legally authorized representatives.

References

1. Mészáros I, Mórocz J, Szlávi J, et al. Epidemiology and clinicopathology of aortic dissection. Chest 2000;117:1271-8.
2. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. J Am Coll Cardiol 2010;55:e27-e129.
3. Umaña JP, Lai DT, Mitchell RS, et al. Is medical therapy still the optimal treatment strategy for patients with acute type B aortic dissections? J Thorac Cardiovasc Surg 2002;124:896-910.
4. Parsa CJ, Williams JB, Bhattacharya SD, et al. Midterm results with thoracic endovascular aortic repair for chronic type B aortic dissection with associated aneurysm. J Thorac Cardiovasc Surg 2011;141:322-7.
5. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA 2000;283:897-903.
6. Boodhwani M, Andelfinger G, Leipsic J, et al. Canadian Cardiovascular Society position statement on the management of thoracic aortic disease. Can J Cardiol 2014;30:577-89.
7. IMPROVE trial investigators, Powell JT, Hinchliffe RJ, et al. Observations from the IMPROVE trial concerning the clinical care of patients with ruptured abdominal aortic aneurysm. Br J Surg 2014;101:216-24; discussion 224.
8. JCS Joint Working Group. Guidelines for diagnosis and treatment of aortic aneurysm and aortic dissection (JCS 2011): digest version. Circ J 2013;77:789-828.
9. Bashir M, Shaw M, Fok M, et al. Long-term outcomes in thoracoabdominal aortic aneurysm repair for chronic type B dissection. Ann Cardiothorac Surg 2014;3:385-92.
10. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373:2103-16.
11. Afifi RO, Sandhu HK, Leake SS, et al. Outcomes of Patients With Acute Type B (DeBakey III) Aortic Dissection: A 13-Year, Single-Center Experience. Circulation 2015;132:748-54.
12. Patel AY, Eagle KA, Vaishnava P. Acute type B aortic dissection: insights from the International Registry of Acute Aortic Dissection. Ann Cardiothorac Surg 2014;3:368-74.
13. Delsart P, Midulla M, Sobocinski J, et al. Predictors of poor blood pressure control assessed by 24 hour monitoring in patients with type B acute aortic dissection. Vasc Health Risk Manag 2012;8:23-30.

14. Melby SJ, Zierer A, Damiano RJ Jr, et al. Importance of blood pressure control after repair of acute type a aortic dissection: 25-year follow-up in 252 patients. J Clin Hypertens (Greenwich) 2013;15:63-8.
15. Fattori R, Tsai TT, Myrmel T, et al. Complicated acute type B dissection: is surgery still the best option?: a report from the International Registry of Acute Aortic Dissection. JACC Cardiovasc Interv 2008;1:395-402.

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