·述评·

The debate of dopamine's clinical application

TIAN Sui-rong(American)

Dopamine (DA) is a hormone in the catecholamine family. It is produced in the brain as a neurotransmitter and is responsible for mood changes including personality, love and euphoria in drug addicts.

DA was first synthesized in 1910 by the British scientists George Barger and James Ewens. In 1958, DA's function as a neurotransmitter was first recognized by Sweden scientists Arvid Carlsson and Nils-Åke Hillarp. For this discovery, Carlsson was awarded the 2000 Nobel Prize in Physiology or Medicine[1].

However, DA rarely is used as a neurotransmitter clinically; rather its vasopressor effects have been widely applied to different clinical scenarios. When it is given as peripheral intravenous infusion, DA activates DA receptor, and α and β receptors for the treatment of shock. The following information comes from pharmacology textbook in my medical school 30 years ago[2].

DA pharmacology: ①Cardiac: activates β1 receptors in the heart, increases myocardial contractility, and cardiac output. ②Blood vessels and blood pressure: activates a receptor in blood vessel and DA receptor with minimum effect on β2 receptor. ③Kidney: dilates kidney blood vessel to increase kidney blood flow, and therefore increases glomerular filtration rate. Also DA can increase sodium excretion and urine output without significant kidney hemodynamic change, which means that DA has direct effect on kidney tubule system.

The textbook also mentions that DA's effects are dose dependant and also depend on the distribution of receptors of target organs. At low dose (intravenous infusion rate at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), DA increases myocardial contractility, selectively constricts blood vessels of skin and skeleton muscle, dilates kidney, splanchnic, and coronary blood vessels by activating DA receptor with minimum blood pressure change. Finally textbook states, "application: shock and combining with diuretics, dopamine can be used for acute renal failure". There is my handwriting on this page where I religiously recorded what my professor told us in the classroom: "use it in patients with cardiac and renal dysfunction." This was my understanding of DA at that time.

Kidney is one of the most important organs in our body and many diseases such as hypertension, diabetes and autoimmune diseases can damage kidney. Protecting kidney is a very important goal during treatment planning.

With the advanced search, we further evaluate DA's clinical effects. During my residency training, I have to study updated textbooks, join journal club discussions and attend different conferences. One day at a lecture given by nephrologist, we were told that we still couldn't find the "magic kidney protection" medication. After years of research, studies show that dopamine doesn't provide benefit to kidney dysfunction. This new knowledge changed my view of dopamine.

In 2000, *Lancet* published a study from Australia and New Zealand. This is double-blind, randomized, placebo-controlled trial for 328 patients admitted to 23 intensive care units (ICUs). Patients have at least one indicator of early renal dysfunction 〔urine output averaging 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ for 4 hours or longer, serum creatinine (SCr) concentration more than 150 μmol/L without premorbid renal dysfunction, or an increase in Scr concentration of more than 80 μmol/L in less than 24 hours without a creatinine kinase level more than 5000 U/L or myoglobin in the urine〕. Patients received either DA infused at a rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or an identical amount of placebo administered through a central venous catheter. The primary outcome was peak SCr level during the study. Secondary outcomes included reason for cessation of trial infusion, development of cardiac arrhythmias, duration of mechanical ventilation, length of ICU stay and hospital stay, peak plasma urea concentration during study infusion, change in SCr and urea concentration from baseline to peak value, hourly urine output at predetermined times, number of

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作者单位:美国纽约西奈山皇后医院麻醉科 通信作者:田穗荣,Email:tinaleungny@hotmail.com

patients requiring renal replacement therapy, number of patients whose serum creatinine concentrations exceeded 300 μmol/L, and survival to ICU and to hospital discharge. Study shows that no significant differences were found between DA and placebo in any primary or secondary outcome measures. The conclusion is: "renal-dose" DA (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) does not appear to confer any benefit to critically ill patients at risk for renal failure[3].

Another meta-analysis in 2001 shows the use of low-dose DA for the treatment or prevention of acute renal failure cannot be justified on the basis of available evidence and should be eliminated from routine clinical use[4].

Despite the fact that DA has been proven to provide no renal protection, my professor told me that we could use DA to treat shock. Do we have new studies to prove or disprove this concept?

In 2006, *Critical Care Medicine* published SOAP Study (sepsis occurrence in acutely ill patients study) which includes 3147 patients with shock from 196 ICUs in Europe. This is a cohort, multiple-center, observation study. Patients were followed up until death, until hospital discharge, or for 60 days. Of 3147 patients, 1058 (33.6%) had shock at any time; 462 (14.7%) had septic shock. The intensive care unit mortality rate for shock was 38.3% and 47.4% for septic shock. Of patients in shock, 375 (35.4%) received DA (DA group) and 683 (64.6%) never received DA. Conclusion of this study suggests that DA administration may be associated with increased mortality rates in shock.

Again, in 2010, *The New England Journal of Medicine* published "Comparison of DA and norepinephrine (NE)in the treatment of shock". In this multicenter, randomized trial, researchers assigned 1679 patients with shock into 2 groups (858 patients receive DA and 821 patients receive NE as first line vasopressor). When the blood pressure could not be maintained with the dose of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for DA or a dose of 0.19 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for NE, open-label norepinephrine, epinephrine, or vasopressin could be added. The primary outcome was the rate of death at 28 days after randomization; secondary end points included the number of days without need for organ support and the occurrence of adverse events. Conclusions show that the death rate is about the same in 2 groups; however, DA group has greater number of adverse events that include arrhythmia ($P<0.001$), open-label vasopressors ($P=0.007$), skin ischemia ($P=0.09$)[6].

Let's look at a meta-analysis published this year to compare DA versus NE in the treatment of septic shock. This study shows that DA is associated with more death and higher incidence of arrhythmia compared to NE[7].

Historically norepinephrine was the first vasopressor used to treat shock years ago. However, due to lack of intravascular volume resuscitation at that time, patients with shock show the signs of worsened tissue perfusion after NE administration because it has stronger vasocontrictive effect. DA is much milder than NE with greater inotropic activity; many physicians accept it as vasopressor of choice. Now time is different; fluid resuscitation is the first-line therapeutic strategy to treat shock before vasopressor application. Many recent studies prove that NE is better drug to treat the septic shock than DA. Personally I rarely use DA nowadays and I know DA is not a common drug used in ICU setting in USA. However, DA has been long used by medical personnel; many doctors are familiar with the medication and feel comfortable for its application, therefore, it becomes part of their routine treatment. SOAP Study shows that dopamine was used more in community than in university or city hospitals (43.6%, 36.3% and 29.9%, respectively, $P=0.016$)[5]. As Dr. David Bracco pointed out in his editorial paper, one French survey showed that in selected clinical situations, the choice of catecholamine is based on personal and cultural preferences, not evidence based. There is some evidence that some community hospital physicians are afraid of NE and believe in DA because DA, "a little bit β and α, as inotrope or vasopressor, may do the job" [8]. With the new strategy of patient management, maybe we need to educate doctors to change their practice according to evidence.

Maybe it is time to abandon dopamine as the first-line vasopressor to treat the patients with shock and "low-dose DA" as the treatment to prevent or treat renal dysfunction.

The controversy of DA's clinical application has been going on for years. Some doctors call DA as "silent killer" while others believe that DA is an "obsolete" medication to treat shock. With further research, maybe we will all come to consensus to this topic and decide the fate of DA.