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Comparison between chemical and mechanical ways of removing thrombus in vivo micro robot

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Abstract. The application of micro-robot in precision medicine is increasing in recent years. Since the particularity of the location of thrombus diseases, it is difficult to remove thrombus by operation, and it may cause some harm to the implementers of the operation. As the size of micro-robots in the body continues to shrink and the accuracy of operation continues to improve, they are expected to reduce the harm of thrombotic diseases to patients and reduce the possible impact by removing thrombus. In this review, we will mainly compare the principle, manufacturing and driving data of two kinds of in vivo micro-robots that remove thrombus chemically or mechanically, and analyze their time and effect of removing thrombus. Several typical in vivo micro-robots used to remove thrombus are discussed and analyzed. Some of their advantages and disadvantages are demonstrated, and the future development direction of in vivo micro-robots for removing thrombus is prospected and some suggestions are put forward.

Keywords: micro robot, thrombus removal, medical micro-robot in Vivo.

1. Introduction

Micro robots have a very broad prospect in helping to treat diseases in complex biological environments. Different from the traditional way that relies on precision instruments such as micro endoscope and requires skilled doctors to perform surgery, the in vivo micro robot can accurately position itself to perform minimally invasive surgery and other precision operations in a complex space by virtue of its tiny size. Stroke and ischemic heart disease are the causes of a large part of deaths worldwide, and thrombosis is a large part of the causes of stroke and ischemic heart disease. At present, the main ways to clear thrombus are to directly aspirate thrombus in vitro or inject drugs such as tissue plasminogen activator (t -PA) to accelerate thrombolysis, but these methods have considerable limitations and implementation difficulties If thrombus is extracted through catheter mechanical device, in this process, medical personnel not only need to be extremely cautious and keep focused for a long time, but also need to be continuously exposed to X -ray for observation and operation. Using micro robot instead of traditional intravascular catheter intervention to clear thrombus can alleviate and effectively avoid the above problems. Therefore, micro robots have been studied in the treatment of thrombotic diseases. Different from traditional treatment methods, the micro robot in vivo can directly reach the affected area for treatment with the help of the driving device along with the blood vessels. In the current research, micro robots that help clear thrombus can be roughly divided into chemical thrombolysis and mechanical thrombus removal according to the

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way of thrombus removal. In this review, we will mainly compare the advantages and disadvantages of several typical micro robots that dissolve thrombus chemically and remove thrombus mechanically.

2. Principle of thrombus removal by micro robot

2.1. Micro Robot for Chemical Thrombolysis

Micro robots that dissolve thrombus chemically through targeted drug delivery are mainly magnetic soft robots controlled by groups, which can actively release substances such as t -PA to accelerate the dissolution of thrombus to clear thrombus For cluster controlled micro robots, magnetic nano particle clusters are generally used, which can be deployed to the thrombus location and released by jointly operating the micro nano machine to transport drugs [1]. Moreover, the rotation of magnetic nano particles can help to clear thrombus to a certain extent. The magnetic nano particle cluster designed by LaliphatManamachaiyapornd's team can capture t -PA molecules from eddy currents, and has verified the possibility of using swarm for thrombolytic therapy. The thrombolytic speed of this micro robot is three times that of using t -PA alone in clinical practice [2].

2.2.Micro Robot for Mechanical Thrombus Removal

The micro robot for mechanical thrombus removal is mainly a soft magnetic robot whose body shape rotates under the driving force or uses catheter guide wire to achieve drilling and other ways to remove blood clots and make blood circulate. A spiral or spiral shaped micro robot with permanent magnets driven by the electromagnetic navigation system (ENS) in three -dimensional (3D) space and rotating by the applied electromagnetic torque is generally acceptable [3].

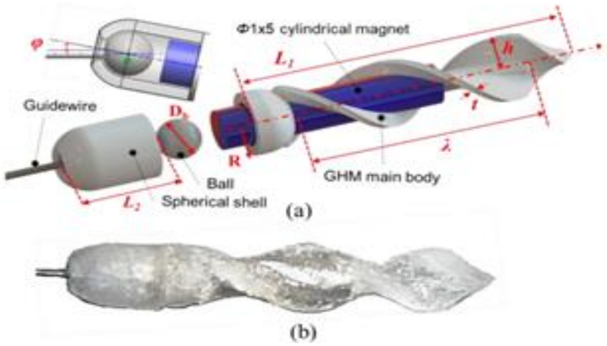

Figure 1. A micro robot with driving force provided by guide wire (a) structural design of the robot (b) manufacturing the robot by 3D printing [4].

The X -ray, which can be used in the operating room and is common, is often used for positioning. Compared with MRI positioning, there will be no interference between magnetic fields, making the tracking more accurate and reliable. AnnaV. Pozhitkova's team designed a programmable soft magnetic robot, which can penetrate and extract thrombus in vitro experiments under the applied magnetic field. It can move normally in different environments and achieve a swimming speed similar to that of animals. Julien Leclerc's team proposed a method to control the internal current of magnets, and proposed a swift robot for fast charging and discharging [5].

3. Comparison of different ways of removing thrombus by micro robot

3.1. Chemical Method

The chemical thrombolytic micro robots are extremely small in size because they are all in the nanometer scale and some of them are compounded by magnetotactic bacteria [6]. This kind of micro robot can be prepared by inducing magnetotactic bacteria to form an aggregation chain, and then arranging it along the center of the droplet sphere, or by cultivating cells in 3D [7].

Most of the driving methods of micro robots that help to treat neurological diseases are magnetic torque driving. Compared with other driving methods, magnetic drive has the advantages of high accuracy, accurate positioning, and the magnetic field used for driving and positioning can penetrate the body harmlessly, effectively, with low distortion or attenuation, so it is widely used in the medical micro robot in vivo [8]. The two kinds of micro robots mentioned in this paper are driven by magnetic field. The permanent magnet in the micro robot is controlled by controlling the external magnetic field strength and magnetic field gradient to achieve the purpose of driving. The micro robot used for targeted drug delivery is controlled in the form of cluster, so it is different from the mechanical micro robot and can use the advantages of cluster to achieve the goal. The micro robot used for targeted drug delivery is controlled in the form of cluster, so it is different from the mechanical micro robot and can use the advantages of cluster to achieve the goal. For example, the diffused nanoparticles can be formed into long chains, which in turn can be decomposed into smaller clusters to control the collection and release of substances [2].

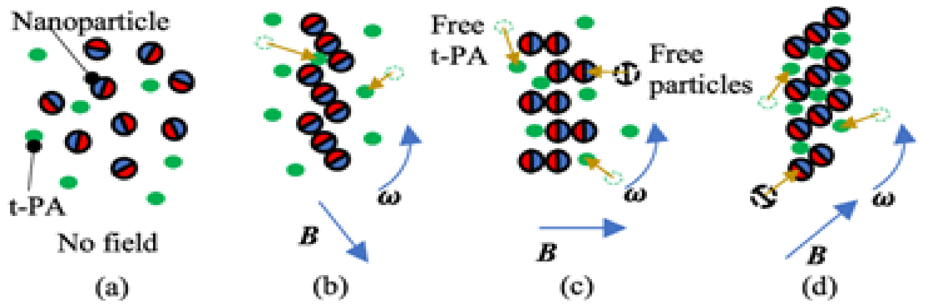

Figure2. Polymerization and Disassembly of Nanoparticle Groups and Capture of t -PA Molecules [2].

In the experiment, the magnetite nano particle group (Fe3O4) proposed by LaliphatManamanchaiyaporn and his team can induce hydrodynamic effects under dynamic magnetic field to capture (t -PA) in eddy current and release t -PA molecules at blood clots. The simulated thrombus used in this experiment is 80 μ L human thrombin was added to 1mLHPPP (human platelet deficiency plasma), and it was dyed light pink, and then it was fully mixed by eddy current. Under the environment with t -PA concentration of 30 μ g /mL. In the experiment, it can be concluded that the higher the concentration of t -PA is, the shorter the time for complete clot removal is [2].

3.2. Mechanical Method

The mechanical thrombus removal micro robot in vivo basically uses its own spiral structure to achieve the goal of thrombus removal through magnetic drive rotation Generally, it can be made of ferromagnetic and elastic materials, while the general spiral micro robot with guide wire can be made of photopolymer jet 3D printer and transparent materials. The driving modes are also different, which can be roughly divided into two types: direct driving by guide wire and electromagnetic torque converted into propulsion force by externally applied rotating magnetic field. The former uses the electromagnetic field generated by the electromagnetic navigation system (ENS), which will interact with the permanent magnet inside the micro robot to achieve the purpose of motion control [9]. In the latter case, the guide wire itself can also provide a part of the driving force. The retraction movement and length of the guide wire itself are provided by the guide wire feeder [10].

In the actual experiment, the reprogrammable magnetic soft robot of AnnaV A Pozhitkova's team can penetrate, hook and extract plasma clots in a simulated vein system with a rotating magnetic field. In the experiment, an equal amount of platelet free normal human plasma (prepared by lyophilized powder according to specifications) was mixed with thrombin solution (4IU /mL), and placed under environmental conditions for about 1 minute to make a simulated thrombus. In the experiment, it takes three minutes to penetrate and hook the fibrin clot of the model, and another 5 -7 minutes to extract the

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clot [3]. It is worth mentioning that in 10 experiments, only 5 cases observed successful thrombus hook and extraction.

Another good example of a micro robot controlled by wire guide is designed by Kim, Tien and others above. In the experiment of this robot, it is an in vivo experiment. The thrombus was produced by injecting 350 μ l9% (w /w) gelatin from the lower part of the inferior renal aorta in mice, while pre clamping the upper part of the inferior renal aorta and the left renal artery to form thrombus. In four experiments, thrombus was successfully formed three times, thrombus was cleared four times, and in two experiments, the subjects survived [9].

It is very difficult for a micro robot driven by a magnet to remove thrombus to resist blood flow and maintain stability while reaching the affected area and drilling holes. In contrast, the robot controlled by wire guide can provide relatively stable driving force and reduce power consumption. However, it is still a complex problem to get the guide wire to the affected area through complex and thin blood vessels.

Table 1. Comparison of principle and thrombolytic effect between chemical thrombolysis and mechanical thrombus clearance micro robots.

Type	**source**	**principle**	**Composition and preparation of simulated thrombus**	**Time consumed to clear thrombus**	**experimental result**	**conclusion**
mechanical thrombus removal	Anna V. Pozhitkova's team	Through the reprogrammable magnetic soft robot, the plasma clot is penetrated, hooked and extracted in the simulated venous system with rotating magnetic field	(In vitro experiment) Mix the same amount of platelet free normal human plasma with thrombin solution (4IU /mL) and place it under environmental conditions for about 1 minute.	Penetrating and hooking model fibrin clots (3 minutes) Further extraction of clots from blood vessels by self propulsion of swimmers with hook clots (5 and 7 minutes)	In 10 experiments, successful thrombus hook and extraction were observed in 5 cases.	Removal of thrombus by mechanical means is fast, and the manufacturing cost is low. There are some clinical practice data to support the feasibility of this method. Chemical thrombolysis has better accuracy and flexibility, which can be more thoroughly solved in the fundamental purpose of thrombus removal, and greatly reduce the possibility of recurrence

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Table 1. (continued).

	Kim, Tien's team	Wire guide screw micro robot simulating corkscrew motion of bottle opener during mechanical artery resection	(In vivo experiment) 350 μ l9% (w /w) gelatin was injected from the lower part of the inferior renal aorta, while the upper part of the inferior renal aorta and the left renal artery were pre clamped to form thrombus	x	In four experiments, thrombus was successfully formed three times, thrombus was cleared four times, and in two experiments, the subjects survived
chemical thrombolysis	Laliphat Manamanchaiyaporn's team	A group of magnetite nanoparticles (Fe3O4), which induce hydrodynamic effects under a dynamic magnetic field to capture (t -PA) in the presence of eddy currents. And release t -PA molecules at the blood clot	(In vitro experiment) 80 μ L human thrombin was added to 1mLHPPP, and it was dyed light pink, and then it was fully mixed by eddy current. Pour a 3mm tube to form a 9mm long clot, and then store the tube at 37 °C for 40 minutes	2 hours and 20 minutes (t -PA concentration is 30 μ g /mL)	The higher the concentration of t -PA, the shorter the time for complete clot removal

4.Conclusion

In this analysis, it can be found that the in vivo micro -robot to help remove the thrombus is quite feasible, it can successfully remove the thrombus in vitro or in vivo experiments, and at the speed of reaching the affected area, the accuracy of location has positive results.

The window period of diseases caused by thrombus is very short. For example, the anterior circulation, that is, the large internal carotid artery embolism, has the best effect within 6 -8 hours, which is the time window. In the window period, the thrombus should be removed as soon as possible to minimize the impact of thrombus on human organs. In the current research, the mechanical thrombolysis micro robot can break or hook the thrombus in a short time. The time consumed for thrombus removal is generally lower than that of chemical thrombolysis, and the manufacturing cost is low. In addition, there are some clinical practice data to support the feasibility of this method.

The chemical thrombolysis micro robot has a high success rate in the experiment. The chemical thrombolysis method can solve the problem more thoroughly than the mechanical thrombolysis method, greatly reducing the possibility of recurrence. In addition, the magnetic soft robot has advantages over the mechanical thrombolysis robot in accuracy and flexibility.

In a word, there are still some difficulties in the wide application of this kind of micro robot in medicine. According to the experimental data, the successful removal of thrombus is not stable, and the driving mode may not keep the micro robot stable for subsequent operations, or the accuracy of the positioning system is not enough, so that errors such as failure to reach the affected area may result in experimental failure. In the future research, we can establish a more perfect three -dimensional navigation system and find a more stable way to clear thrombus. Besides magnetic force, other driving and navigation methods can be tried, such as real -time ultrasonic Doppler tracking and autonomous navigation. In addition, the manufacturing method can be improved to reduce costs and facilitate the promotion of micro robots in the medical field.

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