Cellular and Molecular Biology

Journal homepage: www.cellmolbiol.org

Effect of bFGF gel nano-sustained-release technology on rehabilitation effect of adult heart valve replacement

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ARTICLE INFO

Original paper

Article history:
Received: August 13, 2021
Accepted: November 24, 2021
Published: December 30, 2021

Keywords:
basic fibroblast growth factor;
nano-slow release technology;
heart valve replacement;
mechanism research

ABSTRACT

the Due to the rapid improvement of economic level, aging and lifestyle changes, the incidence of valvular heart disease continues to increase, and the bFGF gel nano sustained-release technology plays an important role in the rehabilitation of adult heart valve replacement patients. The purpose of this article is to investigate the effect of bFGF gel nano-slow release technology on the rehabilitation effect of adult heart valve replacement patients. The research object was selected from all cases of valve replacement surgery from January 2019 to January 2020, and 216 patients were divided into experimental group and control group, the experimental group carried out the sustained release of bFGF gel nanospheres. The experimental group was 49.76±8.13 years old, including 94 cases of rheumatic heart disease, 13 cases of degenerative valvular disease, and 3 cases of congenital valvular disease, a total of 110 cases. Heart performance tests were performed respectively. The results showed that the incidence of atrial fibrillation, left ventricular hypertrophy and ST-segment depression of 0.1m V in the experimental group were 32.19%, 34.48%, and 19.84%, while the corresponding data in the control group were 62.78%, 52.07%, and 45.87%. It can be seen that bFGF gel nano sustained-release technology is of great significance for the rehabilitation of adult heart valve replacement patients.

DOI: http://dx.doi.org/10.14715/cmb/2021.67.6.3

Introduction

Currently, in various types of cardiac surgery, the number of valvular heart diseases is still dominant. Valvular heart disease refers to the abnormal structure and/or function of heart valves and is an important group of cardiovascular diseases. Opening and closing the valve keeps blood flowing forward. Valve stenosis will increase the pressure in the heart cavity, and valve dysfunction will increase the volume of the heart cavity. This long-term hemodynamic change can lead to structural changes and dysfunction of the atrium or ventricle, which ultimately leads to heart failure, arrhythmia, embolism, and other complications. Heart valve replacement is the main treatment for patients with valvular heart disease.

The basic fibroblast growth factor (bFGF) is an important mitogen and inducer of morphogenesis and differentiation. It is involved in the growth and repair of tissue damage during normal physiological and pathological processes. This is the consensus of experts in the medical field. Kumagai found that after using b FGF or BMP-2 alone or in combination for 2 days, human mesenchymal stem cells cultured in vitro showed a significant increase in the number of cells compared to the control group (1). Hiwatashi observed the effect of different concentrations of bFGF on the proliferation of rat bone marrow mesenchymal stem cells. The results showed that 10 ng.ml-1 b FGF may be the best concentration to stimulate the proliferation of rat MSC cells (2). Wong studied the effects of b FGF, IL-1a, IL-3, IL-6 and other cytokines on the proliferation of human MSCs and found that b FGF had the most obvious effect (3). Hagiwara treated the skin damage of nude mice with b FGF and found that the wound area was significantly reduced ($P < 0.01$), and each dose of b FGF can accelerate the healing of skin wounds (4). Zhai's cell cycle analysis revealed that b FGF induces and promotes G0 and G1 phase cells to enter the S phase during the cell cycle transition, resulting in the rapid proliferation of fibroblasts, epithelial cells and vascular endothelial cells (5). In short, the basic fibroblast growth factor (bFGF) as a

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vascular growth factor can promote wound healing and tissue repair, tissue regeneration and nerve regeneration.

Nano sustained release is a technology that changes the structure of a drug or signaling molecule carrier and allows the drug or signaling molecule to be released from the carrier in a specific way, and can maintain a specific effective concentration for a long time. Currently, there are many studies in the medical field. Takehiro demonstrated that TGF-p can be released from biodegradable injectable PGF-p gelatin microspheres coated with polyvinyl alcohol and citric acid, and studied the elastic modulus, flexural modulus and hydrogel mesh parameters (6). Yang's PLGA in vitro experiments showed that rh BMP-2 encapsulated in PLGA can slowly release BMP to maintain an effective local concentration and maintain its biological activity (7). Reimer reported that the modified glucose may also be degraded by glycans. Therefore, the delivery of bioactive agents using dextran-based nanogel drug carriers not only reduces the number of doses but also eliminates the need to remove empty carriers after drug release (8). Gallina believes that acidic gelatin has high-water content and a rapid decomposition rate. Implantation of bFGF under the skin of mice can induce angiogenesis. Due to the high-water content in the gel, the degradation rate is fast, the release of bFGF is fast, and the induction time of angiogenesis is very short (9). Wiktor transplanted bFGF hydrogel under the skin of mice and observed the formation of new blood vessels around the implant. No new blood vessel formation was observed compared to the bFGF-free hydrogel and bFGF water carrier. This may be related to the rapid clearance of bFGF from the transplant site (10). Therefore, there is an urgent need to combine the study of gel nano-slow release technology with the growth factors that play a role in the repair of heart valve tissue.

This article mainly explores the effect of bFGF gel nano-slow release technology on the rehabilitation effect of adult heart valve replacement patients. The research object was selected from all cases of valve replacement surgery from January 2019 to January 2020, and 216 patients were divided into experiments the group and the control group, the experimental group, sustained release of bFGF gel nanospheres. The experimental group was 49.76±8.13 years old, including 94 cases of rheumatic heart disease, 13 cases of degenerative valvular disease, and 3 cases of congenital valvular disease, a total of 110 cases. Heart performance tests were performed respectively. The results of the study showed that the main complications in the early postoperative period of the experimental group included: 26 cases of pulmonary infections, the incidence rate was 23.63%; 18 cases of acute renal injury, the incidence rate was 16.36%; 8 cases of low cardiac output syndrome, the occurrence the rate was 7.27%; 4 cases of atelectasis, the incidence rate was 3.63%. The innovation of this research lies in the first connection between bFGF-containing gel nano sustained release technology and heart valve tissue repair. At the same time, explore the important role played by bFGF gel nano sustained release technology from the aspects of cardiac performance testing and patient efficacy evaluation.

Materials and methods

Study Object Inclusion and Exclusion Criteria

The research object was selected from all cases of valve replacement surgery from January 2019 to January 2020, and 216 patients were divided into an experimental group and a control group, and the experimental group was given sustained release of bFGF gel nanospheres. As shown in Table 1, the experimental group was 49.76±8.13 years old, including 94 cases of rheumatic heart disease, 13 cases of degenerative valvular disease, 3 cases of congenital valvular disease, a total of 110 cases. The control group included 50 patients, aged 50.16±7.93 years, including 92 cases of rheumatic heart disease, 7 cases of degenerative valvular disease and 7 cases of congenital valvular disease.

Table 1. Basic information of the subjects

Group	Rheumatic heart disease	Degenerative valvular disease	Congenital disease
Experimental group	94	13	3
Control group	92	7	7

Inclusion criteria: preoperative combined with color doppler ultrasound and other examinations were clearly diagnosed as rheumatic heart disease, degenerative valvular disease and congenital valvular disease. Exclusion criteria: preoperative myocardial infarction, severe hepatic and renal dysfunction, infective endocarditis, left atrial thrombosis, preoperative cardiogenic shock, cerebral infarction.

Experimental Instrument Materials

Microplate reader, flow cytometer, transmission electron microscope, magnetic heating stirrer, constant temperature oscillator, vacuum drying oven, dimethyl sulfoxide, liquid paraffin, Span-80, dextran T-40.

Experimental Testing Measures

30 ml of paraffin and 1 ml of Span-80 were added to a three-necked flask, flushed with nitrogen, stirred at 400 rpm, and then weighed 1.2 g of DE-GMA. After 5 minutes, 0.4 ml of TEMED is added to the system (11). The temperature is controlled at 30°C and the stirring speed is 400 rpm. After 60 minutes, nanogel microspheres were obtained, lyophilized and sealed at 4°C (12). Adjust the solubility of b FGF solution to 20 / ml, absorb 50 ml, then add 2 mg of nanogel microsphere lyophilized powder, and let stand at 25°C for 1 hour, b FGF is completely absorbed. Freeze-drying nanospheres can carry bFGF gel nanospheres because the volume of the solution is much smaller than the volume required to swell and balance the nanospheres (13). Put the nano-freeze-drying agent of bFGF gel into the refrigerator at 4°C, take it out after 6 months, and observe the indicator.

Accurately weigh 5 mg of lyophilized nanoparticle powder with FGF drug and dissolve in CH2Cl2. After shaking, it was extracted 3 times with HCl (0.1 mol/ml) solution (14). After each extraction, centrifuge with a low-speed centrifuge and take the solution at the top to obtain a hydrochloric acid solution diluted with b FGF (total volume 20 ml). The absorbance of the sample (b FGF diluted hydrochloric acid solution) at 265 nm was measured with an ultraviolet spectrophotometer, and at the same time, the diluted hydrochloric acid solution hydrolyzed by nanoparticles without b FGF was used as a blank control (15). The absorbance value is substituted into the standard curve formula and the concentration-absorbance standard curve to obtain the corresponding b FGF concentration. The experiment was repeated 3 times to calculate the content of bFGF. Calculate the encapsulation rate: encapsulation rate = nano-microsphere encapsulated drug quality / total drug quality in synthesis × 100% (16).

$$EN\% = (1 - \frac{Cf}{Ct}) \times 100\% \quad (1)$$

Accurately weigh 10 mg of drug-loaded nanoparticles into a dialysis bag, add a small amount of simulated body fluid (SBF) solution to form a suspension, bind tightly and place in 10 ml SBF. For dynamic dialysis (frequency 60 r/min), place the dialysis bag in a horizontal thermostatic oscillator at (37.0±0.5)°C, measure the absorbance at 265 nm, and then release it from the nanoparticles at different locations. Calculate the amount of bFGF.

Observation Index

Heart function (NYHA) scoring standard: Grade 1 = There is no activity limit before and after combined heart valve replacement surgery, and daily activities will not cause fatigue, palpitation, breathing difficulties and other symptoms. Usually, patients will start to feel tired and accompanied by symptoms on the 4th floor. Level 2 = Before and after surgery combined with heart valve replacement, there is a slight movement restriction that can be quickly relieved after a rest. Daily activities occasionally have short-term, mild fatigue, panic, difficulty breathing and other symptoms. Usually, patients have symptoms of heart fatigue on the third floor. Level 3 = limited activity before and after heart valve replacement surgery and relaxation after rest. A small amount of daily activities can cause symptoms such as fatigue and difficulty breathing. Usually, patients have symptoms of heart fatigue on the second floor. Level 4 = Activities before and after combined heart valve replacement surgery are significantly restricted, and heart symptoms of heart failure can occur even at rest. Physical exercise may cause symptoms such as fatigue, palpitation, and difficulty breathing.

Data are expressed as mean ± standard deviation. Paired t-tests are used to determine changes in various indicators before and after treatment in the same group of patients. The independent-sample t test was used for comparison between the two groups. Kruskal-Wallis test was used to analyze the comparison of count data between groups. All data were analyzed with SPSS 10.0 statistical software. $P < 0.05$ is significant.

Results and discussion

Comparison between Experimental Group and Control Group

As shown in Table 2, the main postoperative complications of the control group are as follows: 34 cases of pulmonary infection, the incidence rate is

32.07%, 24 cases of acute kidney injury, the incidence rate is 22.64%, and 16 cases of low cardiac output syndrome the rate is 15.09%. There were 10 cases of atelectasis, and the incidence was 9.33%. The main postoperative complications of the experimental group are as follows: 26 cases of pulmonary infection, the incidence rate is 23.63%, 18 cases of acute kidney injury, the incidence rate is 16.36%, 8 cases of low cardiac output syndrome, the incidence rate is 7.27%, lung 4 cases of atelectasis, the incidence rate was 3.63%.

Table 2. Comparison of postoperative complications

Group	Lung infection	Kidney injury	Low cardiac output syndrome	Atelectasis
Control group	32.07%	22.64%	15.09%	9.33%
Test group	23.63%	16.36%	7.27%	3.63%

Effect of bFGF Gel Nano Sustained-Release Technology on Cardiac Performance in Adult Patients with Heart Valve Replacement

Compared with pre-operation, the heart function (NYHA) of the two groups of patients has been significantly improved and basically stable after 1 week, and most patients returned to work or received surgical treatment 1 month after surgery. As shown in Figure 1, the number of patients with different levels of cardiac function scores on the seventh day after surgery in the control group was 15, 34, 28, and 29, respectively, and the number of patients in grades 3 and 4 was relatively large. On the seventh day, there were 56 patients with primary cardiac function in the experimental group using bFGF gel nano sustained-release technology, 23 patients with secondary indicators, 21 patients with tertiary indicators, and only 10 patients with tertiary indicators. This shows that the bFGF gel nano sustained-release technology can effectively stabilize the cardiac function of adult heart valve replacement patients.

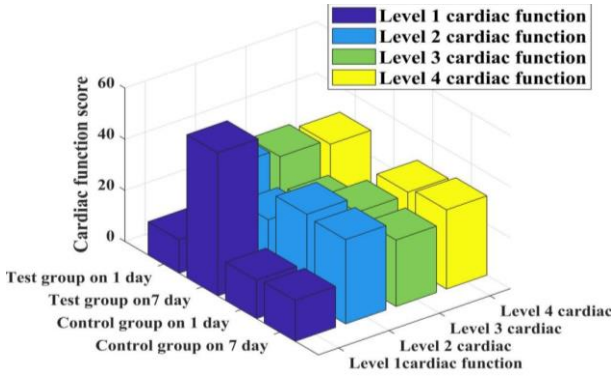

Figure 1. Changes in cardiac function score

As shown in Figure 2, the incidence of left ventricular hypertrophy and ST-segment depression > 0.1m V decreased at different time points after surgery in both groups ($P < 0.05$). In the experimental group, the incidence of atrial fibrillation, left ventricular hypertrophy and ST-segment depression > 0.1m V were 32.19%, 34.48%, and 19.84%, respectively, while the corresponding data in the control group were 62.78%, 52.07%, and 45.87%. This reflects that the bFGF gel nano sustained-release technology can quickly restore the normal physical parameters of adult heart valve replacement patients to normal.

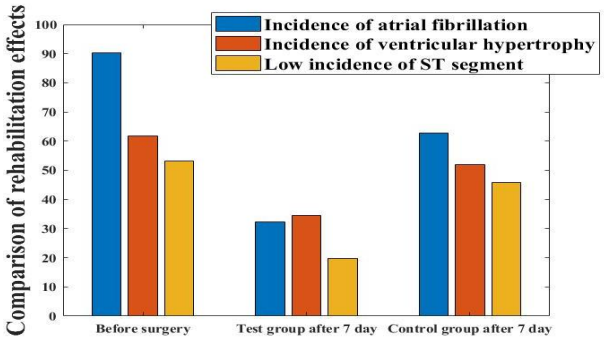

Figure 2. Comparison of rehabilitation effect between the two groups

Rehabilitation effects of bFGF gel nano-slow release technology on adult patients with Heart Valve Replacement

As shown in Figure 3, 56% of the patients in the experimental group believed that the bFGF gel nano sustained-release technology can accelerate the proliferation and recovery of cardiomyocytes, thereby reducing the occurrence of postoperative side reactions. This shows that the bFGF gel nano sustained-release technology can greatly restore the recovery of adult heart valve replacement patients.

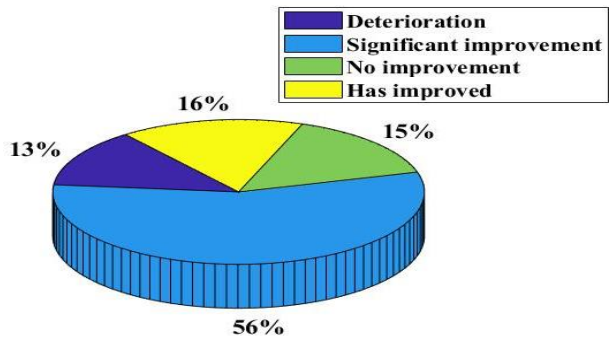

Figure 3. Evaluation of the curative effect of nano-bFGF-containing gel sustained-release technology

As shown in Figure 4, the average blood vessel density before surgery was 29.65/cm2, and the blood vessel density of the experimental group using b FGF nano sustained-release technology was 48.3/cm2. Compared with before surgery, the blood vessel density of the control group also increased to a certain extent. It shows that the blood vessel density of the experimental group carrying bFGF will significantly increase the blood vessel density, and play a key role in promoting blood vessel formation and recovery in adult patients with heart valve replacement.

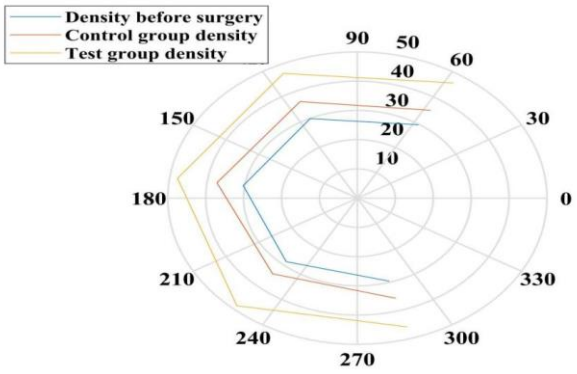

Figure 4. Comparison of changes in blood vessel density

Heart valve disease refers to the abnormal structure and/or function of heart valves and is an important group of cardiovascular diseases. At present, most heart valve replacement surgery still relies on cardiopulmonary bypass, which leads to ischemic reperfusion injury including multiple organs throughout the body, hemolysis, release of inflammatory response factors, and postoperative pulmonary complications of the human neuroendocrine. This is also a major risk factor for acute kidney injury, low cardiac output syndrome and other complications. Therefore, the combination of basic fibroblast growth factor (bFGF) and nano-sustained release technology can induce angiogenesis in ischemic tissues, thereby improving blood circulation and functional recovery in adult heart valve replacement patients.

BFGF is one of the multifunctional cytokines, which has the functions of protecting cells, dilating blood vessels, increasing blood flow and promoting angiogenesis. When the body is injured, the tissue responds protectively to the wound, releasing b FGF, and promoting the division and proliferation of vascular endothelial cells and vascular smooth muscle cells. Use exogenous b FGF to obtain the same effect.

Tissue engineering is the application of principles and technologies in life sciences and engineering (17). Based on a deep understanding of the structure and function of mammals under normal and pathological conditions, research and development have repaired and maintained the science of functional and morphological alternative methods that cause damage to various tissues or organs (18). For tissue engineering, the three basic elements for creating functional tissue are: (1) Three-dimensional scaffold extracellular matrix. It can provide an environment for cell attachment, proliferation and differentiation (19). (2) Seed cells, preferably derived from autologous cells, can provide specific functions required by the tissue. (3) Simulate the signals and stimuli of biological regulators, such as internal environment and growth factors. The basic idea can be divided into in vitro construction and in vivo construction. The general process of in vitro construction is that after the cells are cultured and expanded in vitro, they are adsorbed onto the biological scaffold to form a cellular scaffold spatial complex, and then transplanted to the affected part of the human body (20). As the cells in the lesion grow, the scaffold gradually degrades and absorbs, forming new tissue with normal structure and function, thereby achieving organ regeneration. The general process of tissue construction in vivo is to grow seed cells by culturing and expanding seed cells in vitro, mixing them with biological materials and implanting them directly in the body or re-implanting them after a short period of culture (21). As it is gradually absorbed and degraded by the body, cells continue to secrete extracellular matrix, gradually forming specific tissues or repairing corresponding tissue defects in the body, specifically shown in Figure 5.

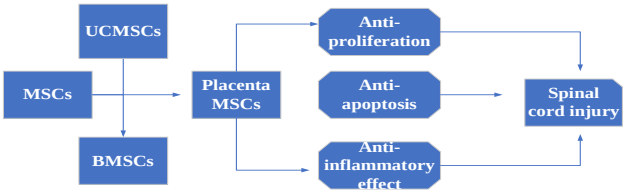

Figure 5. Classification of tissue engineering

As a class of cytokines, growth factors regulate cell metabolism, differentiation, proliferation and apoptosis by binding to specific high-affinity cell membrane receptors, thereby playing a key role in tissue engineering applications (22). It also plays an important

role in repairing damaged tissues, regenerating organs and rebuilding functions. Adding an appropriate amount of growth factor to the biological material and gradually releasing the growth factor can not only induce cell differentiation but also promote cell proliferation (23). The growth factors commonly used in tissue engineering include fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), transforming growth factor growth (TGF-β), bone morphogenetic protein (BMP) and epithelial cells, Growth factor (EGF), hepatocyte growth factor (HGF), nerve growth factor (NGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF) (24). Among them, bFGF is a promoter of cell mitosis during wound healing and plays an important role in the process of functional reconstruction of the damaged body (25).

The incidence of postoperative complications usually affects the rehabilitation of patients undergoing heart valve replacement surgery (25, 26). The main postoperative complications of the control group are as follows: 34 cases of pulmonary infection, the incidence rate is 32.07%, 24 cases of acute kidney injury, the incidence rate are 22.64%, and 16 cases of low cardiac output syndrome the rate is 15.09%. There were 10 cases of atelectasis, and the incidence was 9.33%. The main postoperative complications of the experimental group are as follows: 26 cases of pulmonary infection, the incidence rate is 23.63%, 18 cases of acute kidney injury, the incidence rate is 16.36%, 8 cases of low cardiac output syndrome, the incidence rate is 7.27%, lung 4 cases of atelectasis; the incidence rate was 3.63%.

Studies have shown that bFGF gel nano sustained-release technology can promote the migration, proliferation and survival of vascular endothelial cells and other types of cells, and improve the effects of perfusion and revascularization (23-25). Compared with pre-operation, the heart function (NYHA) of the two groups of patients has been significantly improved and basically stable after 1 week, and most patients returned to work or received surgical treatment 1 month after surgery. The number of patients with different levels of cardiac function scores on the seventh day after surgery in the control group was 15, 34, 28, and 29, respectively, and the number of patients in grades 3 and 4 was relatively large. On the seventh day, there were 56 patients with primary cardiac function in the experimental group using bFGF gel nano sustained-release technology, 23 patients with secondary indicators, 21 patients with tertiary indicators, and only 10 patients with tertiary indicators. This shows that the bFGF gel nano sustained-release technology can effectively stabilize the cardiac function of adult heart valve replacement patients.

Studies have shown that bFGF-containing gel nano-slow release technology can reduce the incidence of atrial fibrillation, left ventricular hypertrophy and ST-segment depression > 0.1m V (21, 23). The incidence of left ventricular hypertrophy and ST-segment depression > 0.1m V decreased at different time points after surgery in both groups ($P < 0.05$). In the experimental group, the incidence of atrial fibrillation, left ventricular hypertrophy and ST-segment depression > 0.1m V were 32.19%, 34.48%, and 19.84%, respectively, while the corresponding data in the control group were 62.78%, 52.07%, and 45.87%. This reflects that the bFGF gel nano sustained-release technology can quickly restore the normal physical parameters of adult heart valve replacement patients to normal.

According to the patient's self-evaluation of the efficacy of bFGF-containing gel nano-release technology to allow patients with adult heart valve replacement, the effect is divided into four levels: significant improvement, improvement, no effect, and worse. 56% of the patients in the experimental group believed that the bFGF gel nano sustained-release technology can accelerate the proliferation and recovery of cardiomyocytes, thereby reducing the occurrence of postoperative side reactions. This shows that the bFGF gel nano sustained-release technology can greatly restore the recovery of adult heart valve replacement patients.

Studies have shown that the addition of bFGF will promote the formation of myocardial blood vessels (24). As the amount of b FGF increases, blood vessel density may increase. The average blood vessel density before surgery was 29.65/cm2, and the blood vessel density of the experimental group using b FGF nano sustained-release technology was 48.3/cm2. Compared with before surgery, the blood vessel density of the control group also increased to a certain extent. It shows that the blood vessel density of the experimental group carrying bFGF will significantly increase the blood vessel density, and play a key role in promoting blood vessel formation and recovery in adult patients with heart valve replacement.

Acknowledgements

None.

Interest conflict

None.

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