

Journal of Advances in Medicine Science

Volume 3 Issue 2 · April 2020 ISSN 2591-7609 (print) 2591-7617 (online)



ISSN 2591-7609



9 772591 760205
Price: S\$30.00

Journal of Advances in Medicine Science

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Address: 12 Eu Tong Sen Street #08-169 Singapore(059819)

Journal of Advances in Medicine Science

Volume 3 Issue 2 • April 2020

International Standard Serial Number: ISSN 2591-7609 (Print)

ISSN 2591-7617 (Online)

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ARTICLE

Study on Opioids Diffusion Based on Improved SIR Model

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ARTICLE INFO

Article history

Received: 26 February 2020

Revised: 6 March 2020

Accepted: 24 April 2020

Published Online: 30 April 2020

Keywords:

Opioids

Diffusion model

Grey relational analysis

ABSTRACT

The abuse of opioids is harmful to the national economy and health. The U.S. government has spent a lot of time, energy and money to deal with this phenomenon. Based on the topic background and team discussion, we deeply excavated the data and information provided in the topic, determined the current use of opioids, and constructed an improved SIR model to determine the source of drug abuse, the mechanism of drug abuse diffusion and the origin of each state through reverse derivation, which provided guidance for the government in the context of opioid abuse. Based on the above results, we simulated and analyzed the improved SIR model and determined the accuracy and stability of the model in the data set.

1. Introduction

In recent years, the mortality rate of opioids abuse in the United States is much higher than that of other causes of death. At the same time, the opioids crisis is also eroding the U.S. economy, involving almost all sectors of the U.S. population, resulting in a series of problems in recent years, such as vacancies in corporate posts, social trust crisis, and the decline in the health-care-assisted economy in the United States^[1]. Effective and accurate judgment of the diffusion of opioids has become the key to controlling the abuse of opioids.

2. Data Preprocessing

2.1 Abnormal Value Processing

If the values in a set of data exceed twice the standard

deviation of the average value, we can call them outliers. In the data provided by NFLIS, we find some abnormal values and use the average value to replace them.

3. Model Construction

3.1 Establishing SIR Model

The SIR model is a propagation diffusion model and it is an abstract description in the process of information dissemination^[2].

Between the five states and their counties are similar to the spread of infectious diseases in the population^[3]. Therefore, SIR model simulation was constructed to study the spread of opioids and the characteristics of opioids and heroin time between the five states and their counties. The total number of people K is unchanged, and the residents of these five states can be divided into three categories:

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(1) There is no abuse of opioids and heroin, but it may be addicted to it, and it is recorded as a susceptible population S.

(2) Abuse of opioids and heroin, recorded as abuse of population I.

(3) The population recovered after abuse is recorded as the recovery population R.

When at time t, S(t) is the number of susceptible people, I(t) is the abused population, and R(t) is the population recovered after abuse. The total number K is constant.

$$K = S(t) + I(t) + R(t) \quad (1)$$

Among them, the infection rate α is the transmission rate of opioids and heroin, and the recovery rate β is the government governance rate.

The infection mechanism of the SIR model is as follows:

$$\alpha : S(i) + I(j) \rightarrow I(i) + I(j) \quad (2)$$

$$\beta : I(i) \rightarrow R(i) \quad (3)$$

When the moment of t+1, the differential equation of S₋(t+1), I₋(t+1), R₋(t+1), propagation process is:

$$I_{t+1} - I_t = dI(t) / dt = \alpha I(t) S(t) - \beta I(t) = \alpha SI - \beta I \quad (4)$$

$$R_{t+1} - R_t = dR(t) / dt = \beta I(t) = \beta I \quad (5)$$

3.2 Determine Parameters

In this paper, the least square method is used to determine the parameters. Based on the known data, the square of the error is minimized and the best function matching of the data is found^[4].

Estimate the given new data, use the first-order Taylor formula to expand, compare the convergence conditions to fit the optimization, determine the distribution law of the parameters, and the sum of the squares of the error between the obtained data and the actual data. Get the parameter result when it is minimum: α : 0.031 and β : 0.87.

4. Application of the Model

4.1 Determining the Birthplace

In order to determine the origin of the use of opioids drugs, we use the 2010-2017 data provided by NFLIS to deduct the parameters of the calculated SIR model and obtain t-1, t-2, t-3, ... The proportion of the number of people

in the SIR model corresponding to the time, under the assumption of the model, the data of 2003 was obtained, which can be used as the birthplace of opioids abuse, combined with SIR model analysis, and the conclusion is shown in Figure 1.



Figure 1. Original place of abuse of opioids

In Figure 1, the red part represents the starting position for the broad diffusion of the opioids. According to the position of the latitude and longitude, the origin of the five states is shown in Table 1 and the probability of the origin.

Table 1. Probability of original place of use of opioids in five states

State	KY	OH	PA	VA	WV
County	ALLEN	CLAY	ERIE	CLARION	CLINTON
Probability	0.7912	0.6331	0.3687	0.5297	0.4107

5. Current Situation Analysis

Opioids are used in medicine to relieve pain in patients. They interact with opioids receptors in cells to increase the patient's pain threshold and reduce the body's perception of pain. They have a strong analgesic effect.

Although society has realized that opioids cause great harm to the human body, there are still many abuses of opioids that exist throughout the world. The main reasons for the analysis re shown in Figure 2 by analyzing drug efficacy and human needs for drugs.



Figure 2. Reasons for the abuse of opioids

6. Model Improvement

6.1 Grey Relational Analysis

The total population, family status, marital status, education level, and ancestral home are all social and economic indicators of the U.S. Census Bureau. We applied grey correlation analysis to study their relationship to the abuse of opioids^[5]. The results presented by the grey correlation analysis method are determined based on the development trend between the influencing factors.

We select the family status, education level and age composition as the research object. Set family status as $x_i(1)$, set education level as $x_i(2)$, set age composition as $x_i(3)$, the abuse of opioids is set as $x_i(4)$, $x_i(4)$ as a reference data column. The grey relational degrees of 2000-2005 and 2010-2015 were calculated respectively, and the changing trends of three influencing factors were analyzed, as shown in Figure 3.

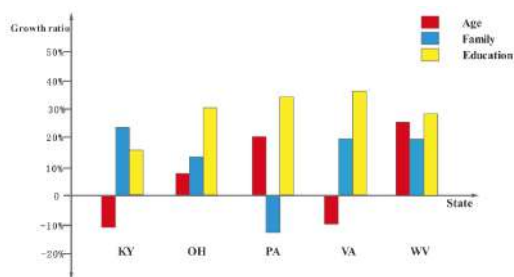


Figure 3. Change of grey relevance degree

According to Figure 3, we found the greatest correlation between opioids use and education. In the analysis of five states, the grey correlation of educational attainment increased.

6.2 Update Parameters

According to the results of grey relational analysis, the factors influencing family status, educational background, age composition and government policy are added to update the parameters of SIR model.

$$S_{t+1} - S_t = dS(t) / dt = -\alpha p I(t) S(t) = -\beta q S I \quad (6)$$

$$I_{t+1} - I_t = dI(t) / dt = \alpha p I(t) S(t) - \beta q I(t) = \alpha p S I - \beta q I \quad (7)$$

$$R_{t+1} - R_t = dR(t) / dt = \beta q I(t) = \beta q I \quad (8)$$

p is a factor influencing the combination of family status, educational background and age composition. Give

different weights, 0.2, 0.5 and 0.3. The calculated value of p is 0.863. q is the influence parameter of government policy. The calculated value of q is 1.748. Determining the parameters $\alpha * q$ and $\beta * q$ of the model is 0.026753, 1.52076.

7. Simulation and Analysis

For the simulation analysis of the improved SIR model, taking 2010 as the starting point, combined with the data provided by NFLIS, the simulation analysis of the model is carried out. Taking Ohio as an example, the results are shown in Figure 4.

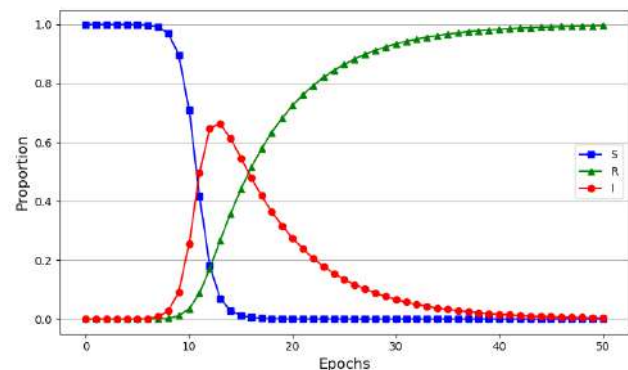


Figure 4. Ohio Model simulation results

According to the analysis in Figure 4, the number of abusers and recoverers of opioids maintained a low proportion at the beginning, and there was a significant increase after the 9th round of diffusion, while the number of people who had not been exposed to opioids also decreased significantly. When the spread reached the thirteenth round, the number of opioids abusers reached a maximum. After continuing to spread, the number of people who abuse opioids has declined, the number of people who recover has continued to increase, and the number of people who do not abuse opioids has dropped to a relatively stable level.

8. Conclusion

In this paper, we analyzed data on opioids abuse in five US states through data, identified the original place of opioids abuse in five US states through improved SIR models, predicted drug spreads, analyzed impacts and proposed improvements. We develop strategies to address the opioids crisis and use our proposed model to assess their effectiveness.

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ARTICLE

Survey and Research on Health Information Assistance Needs of Junior Middle School Students in Different Regions of Guangdong Province

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ARTICLE INFO

Article history

Received: 7 April 2020

Revised: 14 April 2020

Accepted: 24 April 2020

Published Online: 30 April 2020

Keywords:

Junior high school students

Health information

Assistance

Needs

ABSTRACT

Objective: To study the health information assistance needs of junior high school students in 8 different regions of Guangdong Province in a cluster, to understand the current situation of junior high school students' health information assistance needs, and to collect feasibility data for hospitals and schools to jointly promote the healthy development of students. **Methods:** In June 2019, a group of junior high school students from 8 different regions in Guangdong Province [678 students (in 2 towns), 352 students (in 2 counties and prefecture-level cities), and 1098 students (in 4 provincial-level cities)] were selected in a group. A questionnaire survey was conducted by 2128 people, the results of the questionnaire survey were collected, and statistical analysis was performed. **Results:** Of the 2128 junior high school students in 8 different regions, only 52.07% had confidence in their health, and there were no regional differences. Health information for students seeking professional medical assistance includes: 1578 person-times (74.15%) of nutritional diets, 1084 person-times (50.94%) to eliminate tiredness, 1190 person-times (55.92%) to improve sleep quality, 1002 person-times (47.09%) to reduce anxiety, making him happier and stronger 1164 person-times (54.70%). Students in different regions asked for help on how to make their hearts happier and stronger. The results suggest that provincial and county-level students have greater needs than urban students. **Conclusion:** The results of this research show that junior high school students in different regions of Guangdong Province have insufficient awareness of health, and there is a large demand for various health help information, and the focus is on prevention. It is of practical significance to strengthen and meet the health information needs of junior high school students.

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1. Introduction

The junior high school students have just entered the adolescent stage, with obvious changes in their physiology and a big change in their psychology. This is a critical period of physical and mental development^[1], the State Council issued the Opinions of the State Council on the Implementation of the Healthy China Initiative in mid-July 2019, and the National Level launched the Healthy China Initiative (2019-2030). This medium and long-term action focuses on current major health issues and influencing factors. Focusing on the two cores of disease prevention and health promotion, we strive to keep the masses from getting sick and less sick. Based on this background, the researchers found through literature review that most of the previous researches focused on the health problems of junior high school students. For example, because health education is formal, the overwhelming majority of students fail to develop a good health concept, fail to pay attention to personal hygiene, do not like sports, partial eclipse, irregular lifestyles and other bad lifestyles leading to physical weakness, obesity or weight loss, high myopia rate, fatigue, etc. and the heavy learning pressure caused the widespread existence of negative emotions such as psychological anxiety, depression, autism and pessimism^[2-8]. But little attention has been paid to junior high school students' active health information. A survey of health information help needs of junior high school students in 8 middle schools in different regions of Guangdong Province was conducted to explore the current situation of health information help needs of junior high school students. The specific research is as follows:

2. Objects and Methods

2.1 Survey Objects

In June 2019, a cluster sampling method was used to conduct a questionnaire survey on a total of 2128 junior high school students in 8 different regions of Guangdong Province, including 678 students (in 2 towns), 352 students (in 2 counties and prefecture-level cities), and 1098 students (in 4 provincial-level cities). The survey objects included 1108 females, 1020 males, 914 in the first grade, 854 in the second grade, and 360 in the third grade, aged 12-15 years. Inclusion criteria: junior high school students at school who are studying at normal teaching progress without organic diseases. Exclusion criteria: Students who did not return home from school due to an organic disease. All students and their parents who participated in the questionnaire had informed consent.

2.2 Methods and Tools

2.2.1 Methods

The researcher explains the purpose of the survey and the requirements for completing the questionnaire to the students. The questionnaire must be completed independently by the students and their parents with the informed consent. A total of 2128 questionnaires were distributed, and 2128 valid questionnaires were recovered. The effective recovery rate was 100%.

2.2.2 Research Tools

Health Cognition and Health Needs Questionnaire: Due to the lack of attention paid to junior high school students' active help health information in the past, the authoritative questionnaire for junior high school students' active help health information cannot be consulted at present, by referring to relevant research literatures^[9], designed in accordance with the purpose of this research, this questionnaire has been tested by experts and has good reliability and validity. After consulting the experts of the ethics committee of this unit, this questionnaire does not involve personal privacy and does not require approval for filing. The questionnaire contains: 10 items in three parts: general information, health awareness, and health help information (see attachment).

2.2.3 Statistical Analysis

The statistical software "Questionnaire Star" was used for data entry, and SPSS 22.0 software was used for analysis. The counting data was expressed as frequency and percentage. The health needs of students at different levels of schools in various regions took the initiative to ask for help in multiple groups and between groups. $P < 0.05$, considered statistically significant.

3. Results and Analysis

Table 1. Do you think you are healthy? [Single choice]

Options	Total Cases / percent N=2128/100%	Provincial cities N=1098/100%	County-level cities N=352/100%	Towns N=678/100%
A Health	1108/52.07%	592/53.92%	180/51.14%	336/49.56%
B Healthier	720/33.83%	390/35.52%	122/34.66%	208/30.68%
C Fair	250/11.75%	100/9.11%	40/11.36%	110/16.22%
D Unclear	50/2.35%	16/1.46%	10/2.84%	24/3.54%

Table 1 shows that only 22.07% of the 2,128 junior high school students are confident in their health. Different regions show that: 53.92% for provincial cities,

51.14% for prefecture-level cities and 49.56% for cities and towns. According to statistics, $X^2 = 1.77$, $p = 0.41$, the difference is not statistically significant; considering that their health status is only that of ordinary students, the highest is in urban areas (16.22%), followed by county-level cities (11.36%), and the lowest is provincial cities (9.11%). However, the statistical results showed that $X^2 = 2.26$, $P = 0.32$, and the difference was not statistically significant. It can be seen that the students in various regions have comparable self-confidence indexes for their health.

Table 2. Do you agree that health is a prerequisite for us to better work, study, live and realize the value of life in the future? [Single choice]

Options	Total Cases / percent N=2128/100%	Provincial cities N=1098/100%	County-level cities N=352/100%	Towns N=678/100%
A Very agree	1726/81.11%	948/86.34%	268/76.14%	510/75.22%
B Agree	384/18.05%	140/12.75%	78/22.16%	166/24.48%
C Dis-agree	18/0.85%	10/0.91%	6/1.70%	2/0.29%

Table 2 shows that 81.11% of students realize that health is the prerequisite for us to better work, study, live and realize the value of life in the future; there are differences in the recognition that health is the prerequisite for us to better work, study, live and realize the value of life in the future. The provincial level is 86.34%, the county level is 76.14%, and the town is 75.22%. Chi-square test was performed in three groups, $X^2 = 20.3$, $P = 0.00$, and the pairwise comparison. The results of the comparison between provincial students and students at county, prefecture, and town levels showed that $X^2 = 10.5$, $P = 0.001$, $X^2 = 17.62$, and $P = 0.00$. The differences were statistically significant, and the comparison results of county level and town were $X^2 = 0.53$, $P = 0.82$, and the difference was not statistically significant. Prompt provincial students have the highest awareness of health as the prerequisite for us to better work, study, live and realize the value of

life in the future.

Table 3 shows that the content of 2128 junior high school students who wish to receive professional medical assistance includes: nutritional diet, elimination of tiredness, and improvement of sleep quality with more than 50% of the demand; reduce anxiety by nearly 50%; however, the junior high school students in various regions asked for nutrition and diet, asked for help to eliminate tiredness, asked for help to improve sleep quality, and asked for help to reduce anxiety. The results were compared between groups. The results were: $X^2 = 4.85$, $P = 0.09$, $X^2 = 3.31$, $P = 0.19$, $X^2 = 0.40$, $P = 0.82$, $X^2 = 1.30$, $P = 0.52$, the results are not statistically different, suggesting that the demand in this area is similar.

There are differences in how to ask for help to make your heart happier and stronger. The results are $X^2 = 28.59$, $P = 0.00$, the results were statistically different, and the comparison was made pair by pair. The comparison results at the provincial, county, city and town levels were $X^2 = 2.88$, $P = 0.09$, $X^2 = 28.60$, $P = 0.00$, the comparison results between county and city level and town are $X^2 = 5.81$ and $P = 0.02$, suggesting that provincial, county and city level students have greater needs than urban students in terms of how to ask for help to make their hearts happier and stronger. In the last "Other" open-ended question, the proportion of urban students is the highest (20.94%), and the provincial level is low (6.38%). The assistance needs are as follows:

- ① How to regulate the body to make the memory of the mind better and better?
- ② How to manage your body in daily life?
- ③ How to get acne?
- ④ It is recommended that schools hold more publicity on students' physical and mental health.
- ⑤ How can I get out of the bad state quickly?
- ⑥ How to protect your eyes in a stressful study life?
- ⑦ Hand hygiene knowledge.

Table 3. If you have frontline clinical staff coming to your school regularly, which of the following health issues would you most like to ask for help? [Single choice]

Options	Total Cases / percent N=2128/100%	Provincial cities N=1098/100%	County-level cities N=352/100%	Towns N=678/100%
A. What kind of nutrition match will make me healthier and not overweight or thin?	1578/74.15%	810/73.77%	248/70.45%	520/76.70%
B. How can I feel less tired?	1084/50.94%	584/53.19%	160/45.45%	340/50.15%
C. How can I improve my sleep quality?	1190/55.92%	624/56.83%	192/54.55%	374/55.16%
D. Is there any way I can be so anxious and helpless that I am always depressed?	1002/47.09%	524/47.72%	152/43.18%	326/48.08%
E. Is there any way to make my heart happier and stronger?	1164/54.70%	678/61.75%	192/54.55%	294/43.36%
F. Others	258/12.12%	70/6.38%	46/13.07%	142/20.94%

Table 4. Are you happy to share your health knowledge with your family and friends around you? [Single choice]

Options	Total Cases / percent N=2128/100%	Provincial cities N=1098/100%	County-level cities N=352/100%	Towns N=678/100%
A Yes, glad to	1910/89.76%	1014/92.35%	296/84.09%	600/88.50%
B Not very glad	194/9.12%	76/6.92%	46/13.07%	72/10.62%
C Unhappy	24/1.13%	8/0.73%	10/2.84%	6/0.88%

Table 4 shows that the vast majority of 2,128 junior high school students are happy to announce their health knowledge to family and friends around. Provincial cities have the largest number of students, up to 92.35%, and cities and counties at prefecture-level cities are also above 84%. The comparison of the three groups was $X^2 = 10.75$ and $P = 0.01$, and the differences were statistically significant. The comparison results of provincial cities with prefecture-level cities and towns were $X^2 = 10.42$, $P = 0.00$, $X^2 = 3.76$, $P = 0.05$, and the comparison results between prefecture-level and township students showed that $X^2 = 1.99$ and $P = 0.16$. It is suggested that satisfying the need for health information for junior high school students will not only benefit the healthy development of junior high school students, but also help radiate more relatives through the preaching of junior high school students.

4. Discussion

"Healthy China" is a major strategic deployment of the Central Committee of the Communist Party of China for the promotion of the health of all citizens. Talent is the greatest productive force for social development. The healthy growth of young people is directly related to the physical fitness of all future citizens. This research starts from paying attention to the need for junior high school students to actively seek health information in order to provide targeted health assistance measures for relevant departments at higher levels and to provide feasible data for junior high school students' healthy development.

The results of this research show that, although more than 70% of students can correctly understand the meaning of health, 47.93% of them are not confident about their health. Of the 2128 junior high school students, 6276 people issued their medical help for a number of health problems that bothered them, and it is hoped to get professional guidance from front-line medical workers in order to solve their health problems in a timely manner. In their help information, the most involved is the development of physical and mental health. This is in line with previous research by Sun et al.^[10-18] on junior high school students due to the early onset of youth, the unequal awareness of health knowledge, and the school, family, and personal factors caused by health problems such as physical stress, psychological anxiety,

depression. The study by Zhang Yan et al.^[19] showed that factors such as obsessive-compulsive, somatization, depression, and anxiety have a higher correlation with total sleep quality scores. Studies by Chen Jieyu, Qiu Yuming, et al.^[20,21] further showed that lack of adequate sleep, poor sleep quality, sleep deprivation, and the incidence of subhealth are closely related. According to Zhao Runshuan, Ma Ning and other^[22-29] researches on different occupations such as college teachers, company employees, government officials, college students, medical staff and other groups, it found that the prevalence of sub-healthy people is 46-82.4%. From the health help information questionnaire, we found that sub-health problems such as fatigue, poor sleep, psychological anxiety, and depression also existed in junior high school students, with an average prevalence of 55.67%.

Examination-oriented education in China has caused schools, teachers, parents, and students to focus on the study of books, ignoring the healthy development of body and mind. Furthermore, because the medical knowledge of the teachers in the school is far inferior to that of medical staff in professional colleges, which results in a lack of students' health knowledge, many students develop bad lifestyles, causing health problems to become increasingly prominent. The research results show that the junior high school students of provincial middle schools have the highest awareness rate of health importance, reaching 86.34%. How to make the junior high school students in the golden period of physical and mental development grow up healthily is a major public welfare issue facing the whole society, especially in front of medical workers. And it was found in the research that nearly 90% of the students are willing to spread the health knowledge they have learned to their families and the surrounding people, so the students will not only receive health instructors, but also the disseminators of health information.

5. Conclusion

For junior high school students who have just entered adolescence, physical and mental development is very important. If they can get professional medical assistance in time for health problems that they actively seek help, it will be of great benefit to their overall development. It is recommended that relevant departments formulate a

practical and effective long-term mechanism, encourage hospitals and schools to cooperate, timely discover and analyze health help information from students in a timely manner, and formulate measures to effectively solve the physical and mental health problems of students. Medical workers with the latest authoritative expertise are expected to become the most powerful leader of the health promotion movement, and to make their due contribution to the implementation of the national "Healthy China" policy and to reduce the overall medical expenses of the entire population. There are certain deficiencies in this research: in this research, the questionnaires were mostly juveniles. The answers to the questions depended on the subjectivity of the subjects. The results of the research may be biased.

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Appendix

Questionnaire on health cognition and health needs of junior high school students

Dear classmate:

Hello there! In order to complete the subject of the survey of junior high school students' health cognition and health needs, a junior high school student's health cognition and health needs survey was conducted. This questionnaire is of great significance to the research of this topic. The questionnaire is conducted anonymously and has no impact on you and the school. The questionnaire has no standards for the correctness of the respondents. It is only used for scientific research. If you and your parents agree Please fill in truthfully, thank you for your cooperation!

I. Basic Information

1. Your gender is [multiple choice question]

A male

B female

2. You currently live in [fill in the blanks]

3. The school where you are studying is [Multiple Choice Questions]

A provincial city

B prefecture-level city

C county cities

D Town

4. Your class is: [Multiple choice questions]

A junior

B second day

C third grade

5. Do you think it is necessary to ask front-line professional medical staff from the hospital to explain health knowledge for you? [Multiple choice questions]

A badly needed

B needs

C is not required

D doesn't matter

6. Are you willing to tell your health knowledge to your family and friends around you [Single-choice question]

A yes, glad

B is not happy

C is not happy

Health cognition:

1. Your understanding of the word "health": [Multiple choice questions]

A health means good health and no disease

B health means not fat or thin, strong body

C Health is not just free of illness, but a healthy state of

physical, mental, and social adaptation

D health is to run fast, jump high, and go far

E health is to eat well and sleep well

2. Do you think you are healthy? [Multiple choice questions]

A health

B is healthier

C in general

D is unclear

3. Do you agree that health is a prerequisite for us to work, study, live and realize the value of life in the future? [Multiple choice questions]

A very agree

B agree

E disagree

Third, the medical information you currently need to ask for help:

If there are clinical front-line medical staff coming to your school regularly, which of the following professional assistance do you most want to get? (Multiple choice questions)

A. What kind of nutrition combination makes me healthier and not overweight or thin

B. How can I feel less tired?

C. How can I improve my sleep quality?

D. Is there any way to make my heart less anxious and helpless so that I am always depressed?

E. Is there any way to make my heart happier and stronger?

F. Other (please write it down)

ARTICLE

Anti-N-methyl-D-aspartate Receptor Encephalitis Associated with Peripheral Nerve Injury: A Case Report

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ARTICLE INFO

Article history

Received: 8 April 2020

Revised: 15 April 2020

Accepted: 24 April 2020

Published Online: 30 April 2020

Keywords:

Anti-NMDAR encephalitis

Peripheral nerve disease

Multiple peripheral neuropathy

Autoimmune generalization

Overlapping syndrome

ABSTRACT

A patient with Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis presented with quadriplegia and multiple peripheral neuropathy with axonal lesion, confirmed by electrophysiological examination. The muscle strength in the limbs of the patient gradually recovered almost completely, accompanied by the reversal of neuroelectrophysiological symptoms, and the improvement of clinical manifestations, including consciousness, respiration and cognitive function. It was revealed that the neuropathy in NMDAR encephalitis involved motor or sensorimotor nerves more than pure sensory nerves. No autoantibodies were detectable, in contrast to other anti-NMDAR overlapping syndromes. Although the underlying mechanism remains unclear, it may be associated with autoimmune generalization. In conclusion, when patients with NMDAR encephalitis present with severe limb paralysis, the possibility of peripheral nerve damage should be considered.

1. Introduction

Anti-N-methyl-D-aspartate receptor encephalitis is an autoimmune disease caused by the production of anti-NMDAR antibodies in the central nervous system. With the increasing awareness of the disease, anti-NMDAR overlapping syndrome has begun to attract more attention. However, cases with anti-NMDAR encephalitis rarely present with peripheral neuropathy complications. Anti-NMDAR encephalitis is a common autoimmune limbic encephalitis^[1]. However, anti-NMDAR encephalitis with peripheral nerve damage is rarely report-

ed. Patients with anti-NMDAR encephalitis may exhibit symptoms including memory loss, epilepsy, dyskinesia, involuntary movement, disturbance of consciousness and dysfunction of the autonomic nervous system^[2]. The main cause of this disease is the production of antibodies against NMDAR, which is the main excitatory synapse protein in the central nervous system. NMDAR is a glutamate receptor found in cells of the peripheral nervous system^[3]. Excessive activation of this protein can cause acute neuronal death and chronic neuronal degeneration, whereas insufficient levels of activation are associated with mental health disorders^[4]. In the present case report,

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Abbreviations: NMDAR, N-methyl-D-aspartate receptor.

a patient with anti-NMDAR encephalitis presented with prominent quadriplegia. Electrophysiological examination confirmed peripheral nerve damage in the limbs. Following the treatment of the condition by immunotherapy, the symptoms of peripheral nerve damage also subsided. In addition, relevant literature was reviewed and summarized.

2. Case Report

Patient information. The patient, a 21-year old female, complained of intermittent fever for >5 months and was admitted due to consciousness disorder in May 2018. The patient exhibited no apparent predisposition to headache or fever on February 17, 2018, and improved following the administration of oral medication at a local health facility. On the evening of February 27, 2018, the patient suffered from sudden loss of consciousness, double-fold inversion and twitching of the limbs. She was treated with anti-inflammatory treatment (unknown treatment) at a local psychiatric hospital, with no improvement of the symptoms. On March 1, 2018, the patient was transferred to a hospital in Ningxia, diagnosed with encephalitis and given antiviral and sedative treatment, leading to an adverse effect. On March 8, 2018, a sample of cerebrospinal fluid (CSF) was obtained and sent to the Peking Union Medical College Hospital to be tested for NMDAR antibodies. The results were positive (antibody titer 1:100) and the patient was diagnosed anti-NMDAR encephalitis. Two rounds of γ globulin pulse therapy (0.4 mg/kg/day; March 8-12 and 22-26) were administered. The daily methylprednisolone intravenous dose was gradually reduced from 500 to 40 mg, propofol was administered to control epilepsy, and other treatments were given. A tracheotomy was performed on March 15, 2018 due to dyspnea and the patient was put on assisted ventilation. On March 20, 2018, the patient displayed no autonomous movement in the lower limbs, and subsequently in the upper limbs. Further treatment was administered in a hospital in Beijing on April 10, 2018. Two rounds of γ globulin pulse therapy were administered again (0.4 mg/kg/day; April 12-15 and May 5-11). On April 13 and 20, 2018, a lumbar puncture was performed and an intrathecal injection of methotrexate (10 mg) and dexamethasone (10 mg) was administered. Further treatment included 0.75 g mycophenolate mofetil and 1 g levetiracetam twice daily, 2 mg clonazepam Q8h, 25 ml sodium valproate oral liquid to treat epilepsy and involuntary movements, an indomethacin suppository, oral Betaloc to control autonomic nervous disturbance, enteral nutrition, nerve nutrition, airway management. The patient was transferred to the Yuquan Hospital of

Tsinghua University on June 11, 2018, and continued to be treated with mycophenolate mofetil (dose increased to 1 g), methylprednisolone, indomethacin, levetiracetam, metoprolol.

2.1 Physical Examination for Admission

The patient was transferred to the Yuquan Hospital of Tsinghua University on June 11, 2018. The vital signs of the patient were stable. On medical examination, no particular abnormality was revealed. The neurological examination revealed somnolence, shallow coma, no response to questions or instructions, self-opening eyes, the ability to look around, involuntary movements of the mouth, the remaining cranial nerve examination was not successful because the patient was unable to cooperate. Muscle atrophy, lower limb muscle tension, limb muscle strength III grade, double upper limb tendon reflex significantly reduced and double lower limb tendon reflex could not be induced. The Babinski signs of the legs were negative, and there was no indication of meningeal inflammation.

2.2 Supplementary Examination

The CSF examination (March 2, 2018) gave the following results: Protein, 0.27 g/l; sugar, 2.5 mmol/l; chloride, 125 mmol/l; 80 cells; lymphocytes, 94%; monocytes, 3%; and plasma cells, 3%. A 24-h video-electroencephalography (March 4, 2018) revealed severe abnormalities, background persistent wave changes, bilateral persistent frontal-mesotemporal sharp slow wave bursts, and a high-amplitude β -wave rhythm. The results of the test for the NMDAR antibody (1:100) were positive on March 8 and April 11, 2018. A pelvic and abdominal computed tomography (CT) (March 22, 2018) revealed a small amount of fluid in the pelvis and multiple lymph nodes in the abdominal aorta. A head CT on the same day revealed a right occipital lobe punctate high-density shadow and bilateral maxillary, ethmoid and sphenoid sinusitis. On April 12, 2018, the immunoglobulin levels of the patient were 22.06 g/l. In an abdominal ultrasound (April 11, 2018), the liver, spleen, pancreas, kidney and uterus exhibited abnormalities. The first electromyography (EMG) (April 27, 2018; a hospital in Beijing) revealed that motor nerve conduction in the extremities was normal, and the amplitudes of multiple motor nerve waves were decreased. The result of the second EMG (June 25, 2018; Yuquan Hospital of Tsinghua University) was similar to the previous one. The results of the third EMG (August 14, 2018; Yuquan Hospital of Tsinghua University) were improved significantly (Table I). A transabdominal color Doppler ultrasound (June 28, 2018) revealed a cyst in the right ovary with a small

amount of fluid around it. Head magnetic resonance imaging (June 30, 2018) revealed no obvious imaging changes and right mastoid inflammation. CSF biochemical and immunological tests gave the following results (July 5 and 9, 2018): Pane cell positive; no cells; protein, 14.19 mg/dl; sugar, 3.14 mmol/l; chloride, 118.42 mmol/l; IgG (CSF), IgG (S), OB (S) negative, OB (CSF), SOB (CSF) positive. The NMDAR antibody (1:100) was detectable (July 9, 2018). Further immunological tests of the CSF (July 9, 2018) revealed that CASPR2-Ab, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)1-R-A, AMPA2-R-A, LGI1-Ab, GABAB-R-A, GAD65-Ab, GM1-IgG, GD1b-IgG, GQ1b-IgG, GM1-IgM, GD1b-IgM and GQ1b-IgM were negative. MBP levels were high (0.84 nmol/l), and CV2/CRMP5, PNMA2, Ri, Yo, Hu, Amphiphys were negative.

2.3 Diagnosis

Firstly, the patient exhibited conscious disturbance, abnormal mental behavior, epileptic seizures, involuntary movement, hypopnea and dysfunction of the autonomic nervous system. Furthermore, the result of the anti-NMDAR antibody test was positive. Therefore, the diagnosis of anti-NMDA encephalitis was confirmed, based on the diagnostic criteria reported by Graus *et al* [5]. Secondly, following the muscle weakness in the limbs of the patient, lower motor nerve palsy was observed in a physical examination. Multiple motor nerve axonal lesions were confirmed by neuroelectrophysiology, and the condition was diagnosed as multiple peripheral neuropathy (motor nerve axonal damage).

2.4 Limb Weakness and Symptom Improvements

At a period of 1 month after the onset of the disease, the patient first discovered the inability to move the lower limbs independently, and this soon also involved the upper limbs. Test results revealed that the tendon reflex of the upper limbs could not be induced, the symmetry of the lower limbs was decreased, muscle atrophy was observed in the limbs, and the muscle strength was measured at the lowest level (level 0). At 2 months the upper limbs resumed their autonomous functions, and at 3 months the limbs could move independently and the patient was able to walk. At 4 months, free movement was observed in the upper extremities. The patient was conscious, could understand questions and give brief answers, and was discharged from hospital. No autonomous movement in the mouth and face, no definite abnormality of limb sensation was detected. The limb muscle was atrophied, limb muscle strength is complete-

ly normal, limb tendon reflex was positive and pathological reflex was negative. The electromyogram revealed that the amplitude of motor nerve in extremities was decreased, the F wave and H reflex of the tibial nerve were present, no conduction block was observed, there was prolonged latency, and no abnormal sensory conduction was revealed (Table 1).

3. Discussion

Anti-NMDAR encephalitis is an autoimmune disease mediated by anti-NMDAR antibodies, involving the hippocampus and other parts of the limbic system, and the cerebral cortex. Anti-NMDAR antibodies detected in the serum or CSF are specific indicators of anti-NMDAR encephalitis. Since Dalmaul *et al* [1] reported the first case of anti-NMDAR encephalitis in 2007, the knowledge around anti-NMDAR encephalitis has advanced, and the number of clinically confirmed cases has increased.

In the present case report, a patient presented with fever onset, progressive abnormal mental and behavioral symptoms, epilepsy, language disorders, disturbances of consciousness, hypopnea, autonomic nervous system issues and other manifestations. The anti-NMDAR antibody was detected in the CSF, and, based on the diagnostic criteria by Graus *et al* [5], anti-NMDAR encephalitis was considered as a diagnosis. In the present case, obvious paralysis of the limbs was noted, and an EMG confirmed multiple axonal injuries. Following immunotherapy, the condition of the patient gradually improved, with the muscle strength first being restored in the upper limbs, followed by the lower limbs. Consistently, the motor axonal lesions found during the follow-up neuroelectrophysiological examinations also recovered (Table 1). The peripheral nerve damage could be explained by the classic clinical manifestation of anti-NMDAR encephalitis.

The peripheral nerve damage of the patient was also not due to drug poisoning, toxin poisoning or diabetes. As the CSF proteins were not elevated at different stages of the disease, serum ganglion creatinine lipid antibodies were negative, and the EMG revealed no evidence of root lesions, the peripheral nerve lesions in this patient could not be diagnosed as Guillain-Barre syndrome, despite there being a study reporting Guillain-Barre syndrome in patients with anti-NMDAR encephalitis [6]. The paraneoplastic antibody status in the serum of the patient was negative and no evidence of a tumor was observed in the tumor screening; therefore, paraneoplastic syndrome was ruled out.

The reversible peripheral nerve damage in the patient of the present case report was associated with an-

ti-NMDAR encephalitis. NMDAR is a glutamate receptor expressed in the peripheral nervous system. It is therefore understandable that when antibodies against glutamate receptors occur in the central nervous system, abnormal immune responses against these glutamate receptors can also occur. This phenomenon is termed autoimmune panchemistry, first proposed by Xu Xianhao. The theory originated from the discovery of pyramidal tract disease in patients with myasthenia gravis. The explanation was that although myasthenia gravis was mediated by peripheral anti-acetylcholine receptor antibodies, this abnormal immune response could trigger attacks on central nervous system tissue, resulting in pyramidal tract damage. Associated conditions include thyroid disease and rheumatoid disease. Different autoimmune diseases coexisting in the same patient is also known as autoimmune disease superposition syndrome^[7], where other autoantibodies can be detected in the bodily fluids of a patient with an autoimmune disease without presenting the corresponding clinical manifestations.

Many cases of anti-NMDAR encephalitis complicated with other autoimmune diseases or antibodies have been reported. Qin *et al*^[2] reported that anti-NMDAR encephalitis existed in an atypical form and could coexist with optic neuromyelitis or neurosyphilis. Hatano *et al*^[8] revealed that atypical Miller Fisher syndrome is associated with a glutamate receptor antibody. Titulaer *et al*^[9] reported on patients with anti-NMDAR encephalitis who were also diagnosed with neuromyelitis optica. Hacohen *et al*^[10] demonstrated that brainstem encephalitis, leukoencephalopathy following herpes simplex encephalitis, and acquired demyelination syndrome can occur with anti-NMDAR encephalitis. Baheerathan *et al*^[11] discovered 2 patients who were diagnosed with multiple sclerosis following anti-NMDAR encephalitis.

Including the present case, 11 cases of autoimmune encephalitis with peripheral neuropathy have been reported to date. Among these cases, 8 were anti-NMDAR encephalitis and 3 anti-AMPA receptor encephalitis. Of the 9 patients with recorded nerve conduction velocity injuries, 1 exhibited pure sensory involvement, 3 displayed sensorimotor involvement, and 5 exhibited motor or mainly motor involvement. Among the 11 patients reported by Wei *et al*^[2], 3 were anti-Hu antibody positive, of whom 2 were ultimately diagnosed with paraneoplastic syndrome.

Anti-NMDAR encephalitis can be associated with peripheral neuropathy, mainly in the motor or sensorimotor nerves, exhibiting symptoms including limb atrophy and paralysis. Notably, the weakness symptoms may be obscured by clinical manifestations, including a coma. The

clinical management of this condition requires a suitable differential diagnosis, particularly in order to exclude Guillain-Barre syndrome, paraneoplastic syndrome and other common causes of peripheral neuropathy. It is presumed that autoimmune generalization is the possible pathogenesis. In clinical management, it is important to consider the possibility of anti-NMDAR encephalitis complicated with other autoimmune diseases or lesions, and to expand the range of autoantibodies tested (not only ones targeted to the nervous system, but also for conditions affecting other tissues, including the connective tissue and thyroid), which is of great significance for the evaluation of the condition and the prognosis of the patient. It is recommended that future work on anti-NMDAR encephalitis with peripheral neuropathy focuses on finding novel antibodies.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of Data and Materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' Contributions

FH and LH are responsible for statistics and writing articles and coordinate the work of personnel. SZ, MZ, JW, JH and HG are responsible for collecting data and providing advice. LQ and YZ are responsible for reviewing and revising articles. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of Yuquan Hospital of Tsinghua University (Beijing, China). The patients who participated in this research, signed an informed consent and had complete clinical data.

Patient Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Table 1. Information regarding the EMGs performed at Yuquan Hospital of Tsinghua University.

Sensory nerve conduction

Stimulation site	First EMG		Second EMG	
	Conduction velocity, m/s	Amplitude, μ V	Conduction velocity, m/s	Amplitude, μ V
Right median nerve	62.5	28	57.9	16
Left median nerve	62.1	27	56.1	18
Left ulnar nerve	58.5	12	57.8	11
Right ulnar nerve	60.6	14	57.8	11
Right sural nerve	48.6	8.6	53.6	8.3
Left sural nerve	50	6.8	55.6	5.7

Motor nerve conduction

Stimulation site	First EMG		Second EMG	
	Amplitude, mV	Velocity, m/s	Amplitude, mV	Velocity, m/s
Left median nerve				
Wrist	10.5		10.2	
Elbow	9	54.3	8.7	62.9
Right median nerve				
Wrist	6.4 ↓ (71%)		7.7 ↓ (64%)	
Elbow	6.0 ↓ (66%)	55.9	6.6 ↓ (63%)	60.5
Left ulnar nerve				
Wrist	13		14	
Under the elbow	12.7	65.5	14.1	68.8
Upper elbow	12.1	68.8	13.1	71.4
Right ulnar nerve				
Wrist	13.9		13.4	
Under the elbow	13.4	64.5	13	67.7
Upper elbow	13.5	64.7	12.7	71.4
Left tibial nerve				
Medial malleolus	2.4 ↓ (87%)		4.8 ↓ (74%)	
Right tibial nerve				
Medial malleolus	3.3 ↓ (83%)		5.2 ↓ (73%)	
Popliteal fossa	2.8 ↓	43.6	5.1 ↓	44
Left common peroneal nerve				
Mesotarsal	N/A		1.1 ↓ (83%)	
Below the head of fibula	N/A		1.3 ↓	45.3
Above the head of fibula	N/A		1.3 ↓ (75%)	46.7
Right peroneal nerve				
Medial malleolus	0.4 ↓ (93%)		0.7 ↓ (89%)	
Above the head of fibula	0.6 ↓	46.7	1.2 ↓	46.4

EMG, electromyography.

ARTICLE

Intrahepatic Arterial Delivery of Sorafenib Eluting Beads: A Pharmacokinetics Study

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ARTICLE INFO

Article history

Received: 10 February 2020

Revised: 17 February 2020

Accepted: 24 April 2020

Published Online: 30 April 2020

Keywords:

Sorafenib

Transcatheter arterial embolization

Drug bearing microsphere

Experimental study

ABSTRACT

Objective: To determine the slow-release effect of Sorafenib carried beads and its impact on the normal liver of dogs. **Materials and Methods:** (1) To obtain the maximal drug-carrying of beads, different sizes of beads (300-500 μ m and 500-700 μ m) were tried. Five bottles of different sizes of beads were added into 75% solution of Sorafenid-alcohol with different concentrations: Bottle a, 50mg/20ml; Bottle b, 100mg/20ml; Bottle c, 100 mg/40ml; Bottle d, 200mg/40ml; Bottle e, 250mg/50ml. (2) In vivo study: 12 dogs were randomly divided into four groups [group A, Sorafenib carried bead (500-700 μ m); group B, only bead (300-500 μ m); group C, Lipiodol-sorafenib and four dogs in each group. Each group was treated with TAE with emulsion mentioned above. Sorafenib concentration in plasma and liver tissue was determined with HPLC respectively. **Result:** (1) In vitro research: Sorafenib can be dissolved into 75% alcohol and the best concentration for drug-carrying was 100mg/20ml. (2) In vivo study: ① Compared with group D, the Cmax and AUC in plasma in group A and B has a significant statistics difference ($p < 0.05$). ② Sorafenib concentration in liver tissue could be determined in group A in the 3rd day and even after one week while it could not be determined in group D. **Conclusion:** Sorafenib can be carried in DC-Bead in a certain condition. Compared with emulsion with Sorafenib and lipiodol, DC-bead has a definite slow-release function and it is superior to lipiodol.

1. Introduction

Transcatheter arterial chemoembolization (TACE) is the first choice for the treatment of unresectable primary liver cancer and a minimally invasive interventional treatment technology injecting the chemotherapeutic drug-lipiodol emulsion and embolization inactivation tumor tissue into the local tumor supplying artery through

the catheter guided by angiography and other imaging devices. However, there are many shortcomings in using lipiodol as carrier [1-2]: uncontrollability and instability. Therefore, a new drug carrier is urgently needed so as to enhance the sustained-release capability of Sorafenib and improve the capability of tumor inhibition and angiogenesis.

The emergence of new DC-bead provides us with new hope. DC-bead is a kind of drug embolism bead with sul-

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fonate (negative charge in solution) synthesized by N-Fil process based on PVA particles^[3-4]. Through ion exchange mechanism, the new carried DC-bead can absorb and release chemotherapeutic drugs continuously and at a high concentration, so as to kill tumor tissues and reduce the toxicity to normal tissues.

Based on the above principles, we have carried out an exploratory experimental research of Sorafenib (doxorubicin-carried DC-bead) toluene sulfonate. It was found that DC-bead has the mechanism of ion exchange of Sorafenib powder. The structure of toluenesulfonic acid Sorafenib is composed of toluenesulfonic acid and Sorafenib. Toluene sulfonic acid, with acid group, plays the role of material stability; Sorafenib with basic group. In the solution, toluene sulfonic acid and Sorafenib exist in the form of salt, toluene sulfonic acid (SO_3^-) has negative charge, Sorafenib (NH^+) has positive charge. It has the base of ion exchange with DC — Bead (SO_3^-). The purpose of this study is to demonstrate the feasibility of DC — bead carrying Sorafenib powder, investigate its slow-release effect in vivo, evaluate its effect on normal liver tissue and provide experimental parameters for clinical application.

2. Materials and Methods

2.1 Materials

2.1.1 Animals

16 healthy mongrels, 8 males and 8 females, with weights of 15-19kg and provided by Experimental Animal Center of PLA General Hospital. The animal experiment was approved by the Animal Management Committee of PLA General Hospital.

2.2.2 Drug

Biological target preparation - Sorafenib powder. The tablet is provided by Bayer free of charge and refined by the biochemical room of the Academy of Military Medical Sciences.

3. Methods

3.1 In Vitro Pre Experiment: to Observe Whether DC -Bead Has the Function of Carrying Sorafenib

3.1.1 Dissolving Sorafenib Powder In 75% Ethanol

Add raw Sorafenib powder (100mg) into 2ml solution of 75% ethanol for continuous ultrasonic vibration. Then observe the form of Solafenib powder in ethanol solution at different time points (such as 30min, 1h, 2h), and judge

whether it is completely dissolved in ethanol solution. If it has been completely dissolved, we can gradually increase 5 mg per time of Solafenib powder on this basis, and carry out continuous ultrasonic vibration. If it can't be completely dissolved, add 2ml per time of ethanol solution with the same amount of Sorafenib, increase gradually, and continue to carry out ultrasonic vibration.

According to the pre experiment, dissolve 100 mg Sorafenib powder in 75% ethanol, and 20ml ethanol is needed. The solubility is $C = 100/20 = 5\text{mg/ml}$. (Note: This is the maximum dissolved concentration).

3.1.2 Adsorbing Sorafenib with DC-bead (500-700um)

Filter the DC-bead solution through sterile filter paper, filter out the supernatant of DC-bead, put the DC-bead on the filter paper into the prepared sorafenib-75% ethanol solution, and place them in a 4°C refrigerator for full mixing, homogenization and standing for 24h.

3.1.3 Determining Sorafenib Concentration by HPLC Analysis

HPLC analysis conditions: phenomenex C8 column (5μ, 261mmx4.6mmx5um); mobile phase: triethylamine phosphate buffer (990ml of ultra-pure water plus 10ml of triethylamine, adjust pH to 5.4 with phosphoric acid): acetonitrile = 50:50; flow rate: 1.0ml/min; detection wavelength: 261nm; column temperature: 25°C.

3.1.4 Determining the residual Drug Concentration of DC Bead

Firstly, prepare standard solution, and obtain $CX = C_R \times A_X / A_R$, in which standard $C_R = 0.22\text{mg/ml}$, $A_R = 51713977$, which is the peak area of standard. According to the peak area of the sample and the formula, obtain the concentration of the sample is 0.186mg/ml. Determine the content of Sorafenib in the residual solution as $M_{\text{residue}} = 18.6\text{mg}$. After 24 hours of standing, the percentage of DC bear with a diameter of 500-700um will be $\text{DC}\% = (M_{\text{total}} - M_{\text{residue}}) / M_{\text{sample total}} = (100 - 18.6) / 100 = 81.4\%$.

3.2 In Vitro Experiment

3.2.1 Purpose

To investigate the characteristics of Sorafenib adsorbed by DC-bead with different particle sizes, obtain the maximum carrying quantity and the best carrying concentration, and improve the experimental parameters for in vivo experiments.

3.2.2 Experimental Design

Select 5 bottles of DC-bead particles of different sizes (300-500um and 500-700um) and put them into the Solafenib ethanol solution with different concentrations, a: 50mg/20ml, b: 100mg/20ml, c: 100mg/40ml, d: 200mg/40ml, e: 250mg/50ml. Compare the Sorafenib content in different concentrations (e.g. a and b) and the same concentration (a and c), an obtain the maximum carrying quantity of DC-bead of different particle sizes, so as to provide experimental basis for clinical application. In this experiment, the maximum dissolved concentration (100mg/20ml) of 500-700um DC bead is taken as the reference object.

3.2.3 The Carrying Procedures of Different Sizes of DC-Bead and Sorafenib Powder Are Shown in the Vitro Pre-Experiment Steps

3.3 In Vivo Experiment

3.3.1 Experimental Design

Select 12 mongrels with a weight of 15-17kg including 6 females and 6 males, and randomly divide them into three groups according to the random number method with four each group, respectively: group A: DC-bead (500-700um) - Sorafenib group, group B: DC-bead (300-500um) group, and group C: lipiodol Sorafenib group. Conduct transcatheter embolization of the right branch of the hepatic artery, observe the changes of liver function between pre-embolization and post- embolization 3 days, 1 week, 2 weeks and 3 weeks after embolization. Observe the drug concentration in peripheral blood at 10min, 30min, 1h, 4h, 16h, 1day, 2days, 4days, 7days, 10days and 14days after operation. Kill the animals in the three groups at 3 days, 1 week, 2 weeks and 3 weeks after operation respectively, and measure the local Sorafenib concentration of liver tissue after treatment.

3.3.2 Hepatic Artery Intubation Technology (Figure 1, 2, 3, 4)

After intravenous anesthesia, fix an experimental dog in the center of the large animal plate against its back, prepare skin for the right groin, disinfect and cover with a towel, expose the right femoral artery, puncture the femoral artery with a 21g micro puncture needle under the direct vision, introduce a supporting 4f soft sheath (micro puncture system, a product of American COOK), and insert a 4f arterial sheath (24cm, Terumo Corp., Japan). Under fluoroscopy, insert a 4F RH catheter (Terumo Corp., Japan) or a cobra catheter (cordis Corp. USA) into the celiac artery for routine Celiac Arteriography. The contrast medium used for contrast is Euvism (370mg/ml) with

the parameters of 4ml/s, the total volume of 16ml, and the pressure of 300PSI. After angiography (INNOVA 4100, GE, USA) is performed to determine the anatomic details of the hepatic artery, insert a 3F microcatheter (progress, Terumo Corp., Japan) selectively into the right branch of the hepatic artery, and then inject lipiodol Sorafenib emulsion (46mg / 5ml lipiodol), DC-bead Sorafenib microball and DC-bead beads. Among them, DC-bead Sorafenib is carried with Sorafenib- ethanol (100mg/20ml), which can make the carrying quantity of different size particles basically equal, e.g. 73.0-81.4g, and reduce unnecessary waste of Sorafenib. The end point of interventional embolization will be marked by the presence of contrast retention under fluoroscopy. The actual dosage of experimental animals in group A and group C is A 73.130 ± 6.648 , B 71.175 ± 3.650 and D 69 ± 3.464 , $P = 0.5228 > 0.05$.

Remove the catheter and sheath, ligate the right femoral artery and suture the skin after the operation. Keep injecting the gentamicin 20,000 units per Kg of body weight for 3 days

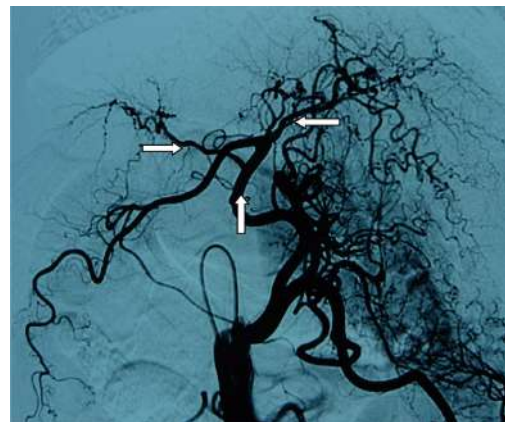


Figure 1. Canine Celiac Arteriography Show: proper hepatic artery (→) and right hepatic artery (↑) and left hepatic artery (←).

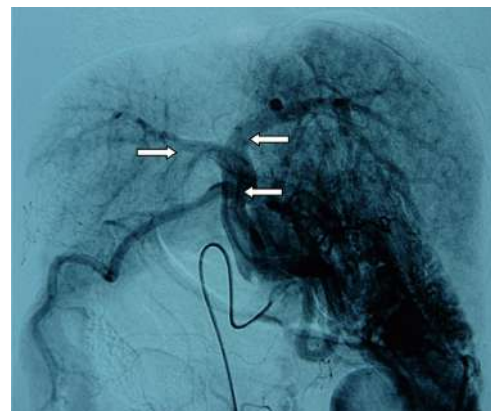


Figure 2. Angiography of the canine celiac artery show: development of the trunk (←) and left branch (←) and right branch (→) in the portal vein phase.

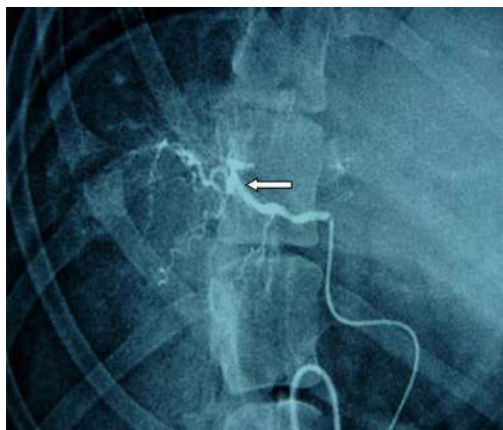


Figure 3. Superselective right hepatic artery embolization with DC-bead-- Sorafenib (←).

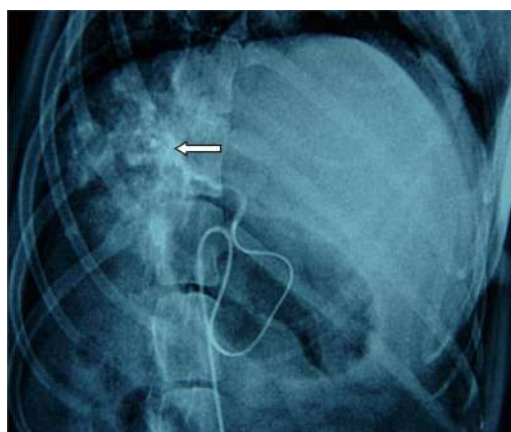


Figure 4. The visible deposition of embolism in the right lobe of the liver (←) after embolization of the right hepatic artery.

3.3.3 Collection of Samples

Observe the peripheral blood drug concentration of experimental animals in different periods of 0 hour (before administration) and 10min, 30min, 1h, 4h, 16h, 1day, 2days, 4days, 7days, 10days, 14 days after operation. Collect blood samples, determine the plasma concentration of Sorafenib by HPLC and investigate the sustained release effect of local administration

3.3.4 Detection of Samples

Determine the concentration of Sorafenib in dog plasma and tissues by HPLC analysis. This part will be completed with the assistance of Pharmacology Research Office of PLA General Hospital.

① HPLC analysis column: chromatographic column: C18 column (10 μ , 250 x 4.0mm); mobile phase: heavy distilled water, water: methanol = 30:70; flow rate: 0.8ml/min; detection wavelength: 254nm; column temperature:

room temperature.

② Preparation of solution:

a. Standard solution: accurately measure 5mg of cisplatin, add normal saline to dilute to 1000ml, and prepare a standard solution with a concentration of 5 μ g/ml.

b. NaOH solution: accurately measure 2G of sodium hydroxide, add distilled water to dissolve and dilute to 500ml, and prepare 0.1mol/l NaOH solution.

c. DDTC solution: accurately measure 0.5g of DDTC, clean with 5ml of ether, dry with nitrogen flow, add 10ml of 0.1mol/l sodium hydroxide solution to dissolve, and prepare 5% DDTC solution.

d. Preparation of Na₂CO₃ solution: accurately measure 1g, add ultra pure water to dissolve and dilute to 100ml, and prepare 0.1mg/ml solution.

e. Preparation of NiCl solution: accurately measure 10mg of NiCl, dissolve it with heavy distilled water and dilute it to 100ml to prepare a solution of 0.1mg/ml.

③ Methods:

a. Processing of plasma sample: 0.6ml of plasma, 0.4ml of 0.5% sodium carbonate solution, 100 μ l of internal standard nickel chloride solution, and 400 μ l of freshly prepared 5% DDTC solution. Keep vortex oscillation for 15s and 37⁰C water for 30min (complexation reaction), and cool down to room temperature. Extract the reaction solution with 2ml of ether, keep vortex oscillation for 5 min, 3000 R / min, and centrifugation for 6 min, and then extract the ether layer. Volatilize in 37⁰C water, dissolve the residue in 200 μ l chloroform and take 10 μ l sample.

b. Tissue sample processing: wash the tissue with normal saline and cut it into pieces. Accurately measure 0.4g (wet weight tissue). Add 100 μ l of internal standard NiCl solution and 1ml of normal saline, cut them into pieces, homogenize in glass homogenizer for 30min, wash the homogenizer with about 1ml of water, and collect about 2ml of homogenizer. Take 1ml of slurry, keep 4000R / min and centrifugation for 4min, take supernatant, and add 400 μ l of 5% DDTC solution freshly prepared. Keep vortex oscillation for 15s, 37⁰C water for 30min (complexation reaction), and cool down to room temperature. Extract the reaction solution with 2 ml of ether, keep vortex oscillation for 5 min, 3000 R / min, and centrifugation for 6 min, and extract the ether layer. Dissolve the residue in 200 μ l chloroform and take 10 μ l sample.

④ Linear relationship test:

Take a proper amount of solution under “ ② a”, add normal saline to dilute it into standard working solution of different concentrations, process it according to the method under “ ② b”, quantitate it with internal standard method, inject 10 μ l in turn, conduct regression analysis on corresponding content (X) with peak area (Y), and obtain

the regression equation: $Y = 0.1861X + 0.0929$, $r = 0.9932$ and the regression equation of tissue concentration: $Y = 0.1361X - 0.0729$, $r = 0.9912$, showing the lowest concentration of Sorafenib in plasma and tissue is $0.1\mu\text{g}/\text{ml}$. In this experiment, it is determined that the linear relationship of Sorafenib is good in the range of $0.1\text{--}10\mu\text{g}/\text{ml}$.

3.3.5 Observation of Other Indexes after Operation

① Observe liver function changes between pre-embolization and post-embolization at 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks after operation.

② Use deep anesthesia to kill the experimental animals at regular intervals (1, 2, 3, 4 weeks after the operation), take out the liver tissue, soak and fix the normal tissue and necrotic tissue with formalin solution, embed them in paraffin, make $5\mu\text{m}$ sections, and make HE staining. Observe the pathological changes of liver tissue in different periods, which will be completed with the assistance of the pathology department of PLA General Hospital.

③ Statistical processing: adopt CHISS statistical software, express all measured by $\bar{x} \pm s$, compare inter-ground data group t inspection or variance analysis (F inspection), and t test will be used when the inter-group variance is not uniform or does not conform to normal distribution.

4. Results

4.1 Characteristics of Sorafenib Carried by DC-bead

It is found that sorafenib toluene sulfonate is not (or extremely difficult) directly soluble in aqueous solution, so ion exchange cannot be completed under this condition. However, it has certain solubility in 75% ethanol solution, thus creating conditions for ion exchange

It can be seen from Table 1 that under the same time and the maximum carrying concentration, the carrying of DC-bead with large particles ($500\text{--}700\mu\text{m}$) is $63.9 \pm 21.7\text{mg}/\text{ml}$, and that of small particles is $57.6 \pm 14.8\text{mg}/\text{ml}$, with statistical difference ($P = 0.01 < 0.05$); under the same time and the same carrying condition, the higher the Sorafenib concentration in 75% ethanol solution, the higher the carrying of DC-bead, however, with the increase of

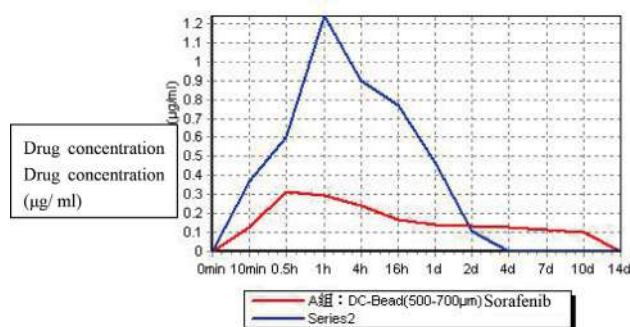
carrying quantity, the carrying rate also gradually decreases. The comparison shows that the maximum carrying of DC-bead with a diameter of $300\text{--}500\mu\text{m}$ is 74.4mg ; the maximum carrying of DC-bead with a diameter of $500\text{--}700\mu\text{m}$ is 82.5mg . With the purpose to prevent excessive loss of residual drugs, the best drug concentration of two different size particles lies in group B ($100\text{mg}/20\text{ml}$).

Table 1. Comparison of carrying quantity of different size particles in different concentrations of Sorafenib ethanol solution in 24 hours (mg/ml)

Group Particle carrying quantity mg um	a (50mg/ 20ml)	b (100mg/ 20ml)	c (100mg/ 40ml)	d (200mg/ 40ml)	e (250mg/ 50ml)
300 — 500	47.1	73.0	68.1	74.4	74.4
500 — 700	48.6	81.4	79.3	82.5	82.5

4.2 The Change and Comparison of Peripheral Blood Concentration of Sorafenib

Between group A and group C. The results show that there are statistical differences in drug release between the two groups. As shown in Table 2, compared with group A, the drug rise rate of group C (Solafenib lipiodol group) is significantly faster than that of the first two groups, and it is rapidly reduced. There are significant differences in C_{max} (0.3 ± 0.06) and AUC (Area Under Curve, $1.82 \pm 0.367\mu\text{g}/\text{mL min}$) between group A and group C (1.24 ± 0.109) and AUC ($2.97 \pm 0.267\mu\text{g}/\text{mL min}$) ($P = 0.002 < 0.05$). In group C, the drug concentration cannot be measured until the 4th day, indicating the instability and uncontrollability of the release of Sorafenib with lipiodol as carrier.



Group A: Curve of changes of peripheral blood drugs in different carriers with Sorafenib

Table 2. plasma concentration of Sorafenib in group A and C after administration ($\mu\text{g}/\text{ml}$, $\bar{X} \pm s$)

Group	10min	30min	1h	4h	16h	1day	2days	4days	7days	10days	14days
A	0.13 ± 0.027	0.13 ± 0.021	0.3 ± 0.055	0.24 ± 0.01	0.17 ± 0.033	0.14 ± 0.020	0.13 ± 0.010	0.13 ± 0.019	0.12 ± 0.007	0.10 ± 0.00	0
C	0.37 ± 0.011	0.6 ± 0.022	1.24 ± 0.109	0.9 ± 0.025	0.77 ± 0.037	0.47 ± 0.021	0.11 ± 0.005	0	0	0	0

4.3 The Change and Comparison of the Drug Concentration of Sorafenib In Group A and Group C

The results show that the drug concentration in the tissues of group C is very low and cannot be measured at three days after the operation, while the drug concentration in group A is significantly increased, and the Sorafenib concentration in the tissues of group A can still be measured at one week after the operation, showing that DC-bead has better controllability in the release of Sorafenib as a carrier.

Table 3. Plasma concentration of Sorafenib in liver tissue after administration in group A and C ($\mu\text{g} / \text{ml}$, $\bar{X} \pm s$)

Group	3days	1week	2weeks
A	4.047 \pm 0.03	1.320 \pm 0.006	0.455 \pm 0.016
C	0.12 \pm 0.06	0	0

5. Discussion

5.1 Feasibility and Mechanism Of DC-Bead Carrying Solafenib

The controllable and sustainably releasing drugs with local high concentration can not only act on the target site, but also avoid other non-target sites from being affected and reduce the occurrence of side effects of systemic medication, being one of the directions in the field of medical development. For instance, in the peripheral vascular interventional therapy, the technique of continuous drug infusion through indwelling catheter is often used to treat thrombotic diseases, continuous vasopressin infusion to treat bleeding cases, continuous infusion of chemotherapy drugs to treat malignant tumors, etc. The drug coated stent frequently used in cardiovascular interventional therapy constantly can release drugs through the drugs inside the stent (e.g. paclitaxel, rapamycin) [5] and along with the constant degradation of drug carrier multimers and play the pharmacological role. The anti-tumor drugs with biocompatible and biodegradable polymer materials as carriers can selectively release drugs in the focus, which can greatly improve the bioavailability of drugs and effectively reduce the toxic and side effects and dosage of drugs. With the development of modern technology, new technical means have been provided for the preparation of different carriers that meet the clinical requirements, and more carried DC-bead have been developed, such as gelatin beads, absorbable polymer beads, nano carried DC-bead, sodium alginate beads, polyvinyl alcohol acrylic beads that can carry Pingyangmycin [6-9].

DC-bead is a hydrogel particle prepared by Biocompatibles, which is biocompatible, hydrophilic, non-absorbable and capable of carrying adriamycin. It is a new drug

eluted embolization bead prepared by modern biological technology. It can simultaneously embolize tumor vessels and continuously release chemotherapeutic drugs to kill tumor cells [1-4].

Drug carrying mechanism of DC-bead: DC-bead is formed by suspension polymerization of acrylic polyvinyl alcohol macromonomer and sulfonate monomer. The formation of covalent bonds transforms the dispersed droplets into insoluble particles. The polymerization starts at the surface of the droplet and forms free radicals. The monomer polymerizes from the outside to the inside, and then forms the cross-linking area on the particle surface. The ion exchange mechanism corresponding to sulfonic acid group is consistent with the charge of particles and drugs. The particles consist of sulfonated hydrogels, which are negatively charged. The carrying mechanism of DC-bead is that the amine matrix of drug (doxorubicin) in the form of hydrochloride is protonated, the whole is positively charged, and the electrostatic interaction between different charges.

According to the principle of ion exchange, foreign scholars have found that in addition to adriamycin, DC-bead can also be carried with other substances with positive charge such as mitoxantrone, irinotecan, topotecan [10-15]. All of the above drugs can achieve the goal of local high concentration and sustained release through in vitro and in vivo ion exchange mechanism, and have achieved good results in experimental and clinical application. Due to the differences of molecular structure and molecular weight, the maximum drug carrying quantity of the above substances is also different, among which adriamycin has the largest drug carrying capacity.

At present, there is no research and report on whether DC-bead can carry Solafenib at home and abroad. By studying the molecular structure of Sorafenib, we found that Sorafenib has the structural basis of exchange with DC-bead. The molecular structure of Sorafenib contains basic sorafenib and acid benzenesulfonic acid. In the solution state, both of them can form salts, i.e. sorafenib with positive charge (NH^+) and benzenesulfonic acid (SO_3^-) in a dynamic equilibrium state. In this state, benzenesulfonic acid (SO_3^-) can exchange with DC-bead (SO_3^-) to form ion exchange, and then make the sorafenib with positive charge (NH^+) and negative DC-bead (SO_3^-) to form salts, and make DC-bead carry Sorafenib successfully. Our in vitro and in vivo experiments further confirm this hypothesis. In vitro experiment, it is confirmed that DC-bead can adsorb Solafenib, while in vivo animal experiment, it is confirmed that Solafenib is controllable and slowly-releasable in the release of Solafenib, which is different from the simple adsorption and release of general

substances. Therefore, we believe that the ion exchange mechanism may be the main role of DC-bead carrying Sorafenib mechanism.

The solubility of drugs is the premise of ion exchange. Sorafenib is a non-water-soluble substance, which is in suspension state in the water for injection, so it is unable to exchange ions with DC-bead. According to the characteristics of its own substances, we found that Sorafenib can be dissolved in methanol and 75% ethanol. The former has higher solubility, but methanol is toxic to human body. Therefore, 75% ethanol with relatively lower solubility is selected to dissolve Sorafenib, so as to prepare conditions for ion exchange.

5.2 Characteristics and Advantages of Carrying Sorafenib with DC-bead as Carrier

Kalayci et al.^[15-16] found that there is no statistical difference between Cmax and AUC of chemotherapy drug carried with lipiodol and systemic chemotherapy, so the effect of traditional interventional therapy is limited by systemic toxicity of chemotherapy drug. The sponge embolization combined on the basis of lipiodol chemotherapeutic emulsion embolization can slow down the blood flow speed, but because many chemotherapeutic drugs are soluble in water, a large number of chemotherapeutic drugs have been rapidly released through the blood during the injection of sponge, and we also confirmed the deficiency of lipiodol as the carrier in the experiment. However, we found that the Cmax of sustained-release Sorafenib with lipiodol as the carrier is smaller than that of lipiodol carried chemotherapy drugs reported in literature, and the release time is hours after carrying, rather than minutes or tens of minutes. Our analysis may be related to the physical properties of Sorafenib. Sorafenib is insoluble in both water and lipiodol. Within 20 minutes after mixing, they can still form emulsion with certain stability, and can form stratification with water. With the passage of time and the impact of arterial blood flow, the clearance of lipiodol and the role of lipid soluble substances in the blood increase rapidly.

The release of Sorafenib with DC-bead as the carrier has more obvious advantages. By analyzing the metabolism trend of peripheral blood and histological drugs in group A (DC-bead, 500-700um-sorafenib group), group B (DC-bead, 300-500um, - sorafenib group), and group D (lipiodol sorafenib group), we found that the Cmax and AUC in group A/B are significantly lower than those in group D, with significant statistical difference. The research of histological concentration further found that the Sorafenib concentration in group A/B could still be measured 3 weeks after the intervention, while the Sorafenib concentration in group D could hardly be measured in

the tissues from 1 week after the intervention. The results show that the carrier of Sorafenib with DC-bead has better controllability and slow release. DC-bead is capable of carrying and controllable release of Sorafenib. This feature has important clinical significance^[17-25]: (1) With DC-bead as the carrier, the release of targeted drugs has the ability to continuously release Sorafenib in local high concentration and slowly, and continuously act on tumor cells and tumor blood vessels. Finally, it can inhibit tumor cells and tumor angiogenesis. (2) When Sorafenib is released by DC-bead as the carrier, combined with traditional TACE treatment, the target is more clear and the effect is stronger in inhibiting tumor blood vessels and tumor growth. Clinical researches have confirmed that TACE combined with molecular targeted drugs (e.g. ENDU) can significantly inhibit tumor growth, improve tumor inactivation level, and prolong the generation time of patients. However, compared with other targeted drugs, Sorafenib has more advantages: (1) it is a multi-target molecular targeted drug, which can inhibit tumor growth and angiogenesis. (2) it has a good synergistic antitumor effect with TACE common chemotherapy drugs (e.g. epirubicin, gemcitabine, cisplatin). (3) compared with oral Sorafenib, the advantage of local medication is more obvious. Clinical research found that TACE combined with sorafenib can control tumor progression and prolong the survival time of patients. However, the high cost of long-term oral medication, the low bioavailability of drugs, the large side effects, and the low objective effective rate have brought serious physiological and psychological burden to patients, making only a few patients can afford it. Local continuous drug use not only has a sustainable effect on the target, but also can improve the drug concentration and enhance the anti-tumor effect within a certain range without causing major side effects. In addition, local medication is expected to greatly reduce the clinical cost of systemic medication. Finally, because of the small toxicity of local drugs, it is possible to improve the efficacy of multiple interventional therapy.

However, the release of Sorafenib from different sizes of DC-bead is different, and is affected by the concentration of Sorafenib ethanol solution. We found that the amount, release rate and duration of Sorafenib carried by beads with small particles are shorter than those with large particles, while Cmax is higher than those with large particles. This phenomenon is not only related to the lower dosage of Sorafenib, but also related to the larger surface area, more negative charges and strong adsorption capacity of the beads. It is suggested that different doses of Sorafenib shall be selected for different sizes of DC-bead beads, and the effect of drug concentration in ethanol

solution on drug carrying shall be considered. In addition, different drug carrying methods also have an impact on the drug's look-around performance. The research shows that compared with the traditional iodized oil drug, the new drug carried particles have longer sustained-release time in peripheral blood and tissue, and have better sustained-release performance.

5.3 Deficiencies of the Research

There are certain deficiencies in this research: 1. In this research, ethanol is used as the solvent to dissolve Solafenib, and the maximum drug carrying quantity is only 82.5 mg, while the solvent used is 40ml, which is not conducive to full contact with the drug carrying. To increase the dissolution of Solafenib in ethanol is one of the directions of future research. 2. This research is based on the normal liver tissue instead of blood rich liver tumor model, so how to inhibit the liver tumor still needs to be further researched. We will improve the detection of VEGF, MVD and image in the tumor model of tumor bearing rabbits in the next step, so as to further evaluate the effect of DC-bead drug Sorafenib on malignant tumors (e.g. VX2 tumors).

6. Conclusion

The new Sorafenibcarried DC-bead is feasible in preparation technology, exact in the sustained-release effect, and superior to the carrying effect of lipiodol.

The safety and effectiveness need further research.

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REVIEW

The Number of Five Basic Elements' Motion of Traditional Chinese Medicine and Cancer Prediction

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ARTICLE INFO

Article history

Received: 10 February 2020

Revised: 17 February 2020

Accepted: 24 April 2020

Published Online: 30 April 2020

Keywords:

The number of five basic elements' motion

Cancer prediction

Congenital pathology

Acquired pathology

ABSTRACT

"The number of five basic elements' motion" varies according to the date of birth, which is tightly tied to human health. To predict cancer with "the number of five basic elements' motion" is simple, accurate, worth of research and popularizing.

The theory of "five basic elements' motion and six climatic changes" is a key part of Traditional Chinese Medicine, "the number of five basic elements' motion" is strongly related to the physiology and pathology of human body. Combine with folk pathology prediction, "the number of five basic elements' motion" has been proved to have some scientific validity and of high accuracy in cancer prediction, it is worth to study, research and be discussed in-depth.

1. Introduction

In <Internal Classic of Yellow Emperor (Huang Di Nei Jing)>, it created the theory of "five basic elements' motion and six climatic changes" on the basis of the principle of "Comparative states", revealed the fundamentals of pathology prediction theory of Traditional Chinese Medicine for thousands of years. In recent years, I have conducted a preliminary study and research on this, my research results are as follows, please feel free to give your comments and suggestions, thank you!

2. Clinical Observation on the Prediction of Cancer with "The Number of Five Basic Elements' Motion" of Traditional Chinese Medicine

In <Internal Classic of Yellow Emperor, Plain Questions> "Chapter 66, Great Theory on Law of Primordial Qi in

Nature", it points out: The five evolutive phases and Yin-Yang are the principles of heaven and earth circles, the laws of life and death in the universe, the source of all changes, and the important rules about life & death that we must know. ^[1]



Figure 1



Figure 2

*The cover of <Internal classic of Yellow Emperor> and related illustrations

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In my humble opinion: the five basic elements, Yin-Yang, are the general rules and guides of natural changes, everything has both side of Yin and Yang, and could be summarized with five basic elements: soil, water, gold, fire, and wood, so does the birth date of each person. Different birth date has different Yin, Yang and five elements, it represents in the generation and restriction number of five basic elements' motion; the changes of generation and restriction of the number of five basic elements' motion allows us not only to know the congenital pathology and acquired pathology of human ,but also could predict cancer.

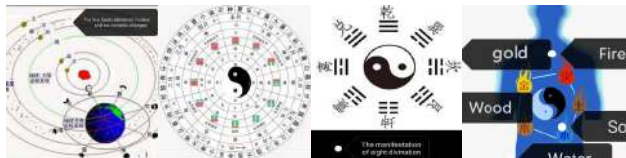


Figure 3

* “The five basic elements’ motion and six climatic changes”& “ Yin-Yang and Five Basic Elements”

Based upon the fundamentals of “five basic elements’ motion and six climatic changes” that established in < Inter al Classic of Yellow Emperor >, I use the number of five basic elements’ motion to predict cancer in combination with the folk birth date prediction. I mainly reserved and predicted 580 person in recent years, it is found that out of 373 general patients that were not confirmed cancer ,179 were at risk of cancer, who were compared with the “Four Diagnoses and Eight-Principles” in Traditional Chinese Medicine , they all have the clinical features of cancer, namely, they have ecchymosis on face, hand, ear or other body parts, some patients have unusually increase of tumor markers. To further verify the reliability of this method, with the same method I verified 89 patients out of the 580 who have been diagnosed , the accuracy reached 95%. Among these 89 patients, 51 are male and 38 are female, among the youngest patients, one aged 7 years and 9 months, one aged 12 , one aged 17; and 41 aged 30-59 , 42 aged 60-79 , 2 aged 80-90 ,and the eldest one aged 98 .

Among these 89 cases, 19 were lung cancer patients, 11 were liver cancer patients, 8 were breast cancer patients, 5 were gastric cancer patients; and patients of colon cancer, pancreatic cancer, leukemia, endometrial cancer and bladder cancer were 4 each, patients of renal cancer and cervical cancer were 3 each; patients of cardiac, rectal, nasopharyngeal, laryngeal, pelvic, and non-Hodgkin’s lymphomas were 2 each; in addition, patients of esophageal, colon, esophageal cancer, bowel cancer, gallbladder cancer, thyroid cancer, oropharyngeal cancer, gingival cancer, prostate cancer, and multiple myeloma were 1 each.



Figure 4

* The illustrations of cancer ecchymosis



Figure 5

* The illustrations of cancer ecchymosis

2.1 Typical Case 1

Xiong X, female, aged 66, admission time: 26th,-Dec.,2018, no noticeable symptoms. Immediate diagnosis: slow pulse, dark red tongue, blue veins under the tongue are bruise, thin white tongue. Hand diagnosis: lung dryness, Yang deficiency in spleen and kidney, has hazel ecchymosis on Hegu acupoint of left hand and slight brown spots on upper warmer of right ring finger, there was a suspected danger of cancer. Hence asked about her birth date for prediction: this person was born on 4th July, 1952; in Chinese Lunar Calendar, that is the thirteenth day of leap May ,the year of the Dragon , the congenital pathology of her number of five basic elements’ motion is”gold restricts wood”, “wood restricts soil,” this indicates there is potential disease in liver, spleen and lung channel; her acquired pathology is “two gold restricts one wood”, which means there are two “11” restricts “4”, 11-4=7, this shows there is potential danger of cancer ,so reminded her to prevent cancer.

However, the patient didn’t take it serious as there wasn’t any discomforts. Unexpectedly, she was suspected to have “breast cancer” during the physical exams on 23rd Oct, 2019, and was confirmed after 2 days, then was hospitalized for surgery and treatment.

2.2 Typical Case 2

The number of five basic elements’ motion of Steve Jobs, the president of Apple Inc ., he was born on 24th Feb.,1955, that is the 24th of the second lunar month of the year of Goat (the year of the soil motion) in the Chi-

nese calendar .His number of five basic elements' motion shows there is a congenital missing of gold, wood, and fire, and deficiency in lung, liver as well as heart. The congenital pathology of his number of five basic elements' motion is "soil restricts water", spleen and kidney are susceptible to diseases, his number of five basic elements' motion is $8-2=6$, 6 pertains to fire and is subsumed to heart, all cancers have something to do with mindset, because "soil restricts water", therefore, he is susceptible to cancer of the digestive system or urinary and reproductive systems; and there is a missing of gold, wood, and fire in his acquired pathology ,deficiency in lung, live and heart; his number of five basic elements' motion is also "soil restricts water" with a subtraction results of 6 ,this indicates he is liable to cancer of the digestive system or urinary and reproductive systems. As both his congenital pathology and acquired pathology show he is at risk of cancer, Jobs got cancer in 2003 the year of the soil motion, took surgery in 2004 the year of the soil motion, and liver metastasis was detected in 2007, even a liver transplantation didn't change his fate, because all these were clearly showed on the ecchymosis of his left liver; according to his "number of five basic elements' motion", his disease will relapse or aggravate in "year of the soil motion " or "year of the wood motion", as expected, it relapsed in 2010 the year of the soil motion, and was considered of no value for continuing treatment, in the end Jobs passed away on 5th Oct., 2011(the soil day, soil month of the year of the wood motion).

2.3 Typical Case 3

Fu Biao, a public figure, male, 42, born on 27th Sep.,1963, that is 10th of the eighth lunar month of Guimao Year in the Chinese calendar. To predict with the number of five basic elements' motion, there is a missing of water and fire in his five elements of congenital pathology, deficiency in heart and kidney, and because wood restricts soil, liver and spleen are liable to diseases; gold restricts wood, liver and lung are susceptible to diseases, his number of five basic elements' motion is $10-4=6$, which indicates he is at risk of cancer; there is a missing of fire and soil in the five elements of his acquired pathology ,and deficiency in both heart and spleen. The prediction results are in accord with the actual situation. After got cancer, Fu Biao had undergone two liver replacement operations, nevertheless, he finally passed away in 2005 the year of "gold motion", because "gold restricts wood"...

2.4 Typical Case 4

Zhan X, female, born on 21st Dec., 1962, that is 25th of

the eleventh lunar month of RenYin year (year of the Tiger) in the Chinese calendar. In her number of five basic elements' motion" soil restricts water", which indicates she is susceptible to spleen and kidney disease, and the subtraction of her congenital pathology and acquired pathology restriction number equals to "6" and "7" respectively , this shows she is predisposed to cancer. She got cancer in 2011 and undergone the radical nephrectomy, however, she got diagnosed with bone metastases the next year; in Sep. 2012, several hospitals said she would only survive for up to 3 months, she then came to our hospital for treatment, the cancer genes were cleared after treated with Chinese medicine and folk herbs, and is still under treatment so far.

3. The Theory of "Number of Five Basic Elements' Motion" and Folk Pathologic Prediction

<Internal Classic of Yellow Emperor ,Plain Questions>, "Chapter 67, Great Theory on Movement of Five Phases" says: I have heard you talking about the laws of five evolutive phases, what you said means the Qi of five evolutive phases governs one year each, as regards to the problem of the cycle of 60 years and definition of evolutive phases, I will discuss with Guiyu Qu... The number of Yin & Yang is countable, it is the Yin & Yang in human body, so it accord with the accountable number of Yin and Yang^[2]There is a comprehensive discussion bout the "number of five basic elements' motion " in the book, it means the Yin, Yang, Qi, and Yun varies each year from "gold motion", "wood motion", "water motion", "fire motion" to "soil motion" , there is not explicitly statement about the number they represent in <Internal Classic of Yellow Emperor >, however, there are corresponding rules about judgement in the folk prediction, for example, for person born in "Zi" year, the earthly prop corresponds to rat, its number is "1", which belongs to "water", "hexagram Gen"; for person born in "Chou" year, its earthly prop corresponds to "ox", the number is "2", belongs to "water", "hexagram Gen"; for person born in "Yin" year, the earthly prop corresponds to tiger and its number is "3", its five evolutive phase and six climatic factors belong to "earth", "hexagram Gen"...the rest person who born in different year each has different animal zodiac, hexagrams as well as different five basic elements' motion and six climatic changes , the numbers it represents differs as well.

The twelve earthly prop and fate are different each year with different "number of five basic elements' motion". But unlike <Internal Classic of Yellow Emperor >, the folk prediction make analysis on the luck of birth date & hour,

and have corresponding provision for the number, the number of luck are the same with that of year, while the hour of birth were stipulated as per the “traditional twelve hour periods”, for instance, “zi shi” [period of the day from 11 p.m. to 1 a.m.] is water ,its number of five basic elements’ motion is “1”, “si shi” is fire, its number of five basic elements’ motion is “6”,etc.



Figure 6

* The illustrations of the “Celestial Bodies Backbone and Earthly Prop”

With regards to the principle of prediction, <Internal Classic of Yellow Emperor, Plain Questions> points out: The harmony between host climatic Qi and guest climatic Qi means health, otherwise, will get sick^[3]. The notes of this passage give a clear explanation of it: “wood adjacent to fire, gold adjacent to water, water adjacent to wood, fire adjacent to soil, soil adjacent to gold, get on well together; soil adjacent to wood, soil adjacent to water, soil adjacent to fire, fire adjacent to gold, gold adjacent to wood, doesn’t get on well together. When the upper adjacent to the lower means smooth, and the lower adjacent to the upper means inverse, inverse will lead to depression and disease, such as soil adjacent to sovereign fire or ministerial fire, etc. It clearly points out that generation among five elements means smooth, the restrictions of five elements means disease. This principle is followed by the folk prediction, however, it defines “congenital pathology” and “acquired pathology” respectively, namely, on the basis of the number of “congenital pathology”, to add or subtract with “the multivariable number 6” depending on the figures, to form the “acquired pathology”, in this way, the number of five basic elements’ motion of the birth year, month and date could be calculated, hence it is able to predict diseases according to the generation and restriction relationship of five elements of the numbers it represents. When the five elements are complete and each element promote the other means health, when they are incomplete or restrict the other means poor health or diseases; if two elements restricts one elements means cancer, e.g.: two wood restricts one soil, two gold restricts one wood; when the subtraction results of five elements restriction number is “6” or “7” means cancer as well, these two numbers ,one is Yin and the other is Yang, they both pertains to heart, fire, because all tumors and diseases can be judged according to the relationship of “five elements” represented

by its number which reflects the health condition, disease and cancer is closely connected to human mentality. (the method of judgement subjects to the number of five basic elements’ motion of birth year, month, day and hour; or subjects to calculated date in case specific birth date is unknown).

4. A look at the Principle of Predicting Cancer with “The Number of Five Basic Elements’ Motion”

The theory of “five basic elements’ motion and six climatic changes” in <Internal Classic of Yellow Emperor, Plain Questions> originates from <The Scriptures of Changes>.



Figure 7

* <The Scriptures of Changes>

In <The Scriptures of Changes, Xici> , it says “Yi is the creation rule of heaven and earth, therefore it includes the operation laws of the world. Look up to view the astronomy, and bend down to observe the geography, so can learn the truth about light and darkness. Observe the start to conclude the result, so know the truth about life and death “. This tells us that the principles in <The Scriptures of Changes > conforms to the principles of heaven and earth, therefore, it include the laws of everything in the universe, the saints look up to observe the changes of celestial bodies and lean down to study the physics of the earth, so they are able to know the subtle changes, study the beginning to conclude the result, so they understand the doctrines of life and death. Born in the world, human is influenced by celestial objects and the earth, the most important of which is the influence of celestial magnetic field and earth magnetic field on human Qi and blood. Just as defined in <Internal Classic of Yellow Emperor ,Plain Questions> , “Chapter 74, Great Theory on Crucial Principles”: What belongs to heaven is the Qi of heaven, and what belongs to earth is the Qi of earth. When the Qi of heaven and earth combines, the division of six climatic factors come into being, and give birth to all lives

on earth^[5]. The “ Qi of the heaven” here is the magnetic field of celestial bodies; “Qi of the earth” is the magnetic field of the earth. The magnetic field of celestial bodies has different properties according to its orbits, in <Internal Classic of Yellow Emperor >, “Chapter 67, Great Theory on Movement of Five Phases “ , it points out: The fire Qi passes through Abhijit, Girl, Mirach, and Alpheratz lunar Mansions; the soil Qi passes through the Antares, Tail ,Horn, and Chariot lunar Mansions; the wood Qi passes through the Rooftop, Encampment, Willow and Ghost lunar Mansions; the gold Qi passes through the Neck, Root, Hairy head and Net lunar Mansions ; the water Qi passes through the Extended net, Wings, Bond and Stomach lunar Mansions.^[6] Five different kinds of “Qi” generates different magnetic fields, which have a profound effect on human’s health since birth. The interaction of magnetic fields between celestial bodies and the earth brands on human body deeply and determines the deficiency and excess of the internal organs, it contains not merely the life genes of human body, but also the congenital and acquired pathology; the date of birth determines the recessive or dominant pro-oncogenes of human body; cancer is not primarily caused by gene mutations, but because proto-oncogenes are activated. The root cause of cancer lies in the imbalance of Yin - Yang which leads to the ac-

cumulation of stasis and toxin in human body, and eventually results in cancer. To predict cancer with the number of five basic elements’ motion does have some scientific validity, which lays the foundation for early prevention and treatment of cancer, it is worthy of further discussion, research and application.

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REVIEW

Analysis and Nursing Health Education of Current Status of Maintenance Hemodialysis Patients with Hyperphosphatemia

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ARTICLE INFO

Article history

Received: 8 April 2020

Revised: 15 April 2020

Accepted: 24 April 2020

Published Online: 30 April 2020

Keywords:

Hemodialysis

Hyperphosphatemia

Nursing health education

ABSTRACT

Concerned about the current situation of hemodialysis patients' awareness of the problems related to dialysis complicated with hyperphosphatemia, further analyze the existing problems and causes, give targeted and individualized health education, improve the compliance of diet, medication and self-management, strengthen nurse-patient communication, establish a good nurse-patient relationship, reduce and control the incidence of hyperphosphatemia, improve patients' quality of life, and improve prognosis.

1. Introduction

Human serum phosphorus concentration is mainly regulated by the kidneys, bones, and intestines. Maintaining normal blood phosphorus is important for normal bone metabolism and cell function. Hyperphosphatemia is one of the major complications of patients with chronic kidney disease (CKD), especially maintenance hemodialysis (HD). A large amount of evidence shows that in addition to hyperparathyroidism, abnormal mineral and bone metabolism, chronic hyperphosphatemia during CKD can also cause metastatic calcification of the heart muscle, heart valves, blood vessels, soft tissues, and these pathophysiological changes not only cause a lot of clinical manifestations of CKD, reduce the quality of life of patients, but also are associated with a high incidence of cardiovascular complications

and increased mortality of patients^[1]. The incidence of hyperphosphatemia is relatively high, and it is reported to be 40%-50%^[2]. In March 2019, our center conducted a questionnaire for patients with hyperphosphatemia on 249 maintenance dialysis patients with independent self-care ability. The results showed that: in terms of disease knowledge, the error rate was 29%;

In terms of diet knowledge, the error rate is 59%; for drug knowledge, the error rate is 38%; for self-management, compliance is poor, which shows that patients with maintenance dialysis have insufficient awareness of hyperphosphatemia. To this end, the health education team of the Department of Nephrology (Blood Purification Center) used patient education activities to specifically strengthen missionary education, which is summarized as follows:

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2. Aspects of Disease Knowledge

Hyperphosphatemia is the main complication of maintenance hemodialysis patients. At present, in addition to causing hyperparathyroidism, abnormal mineral and bone metabolism, it can also cause metastatic calcification of the heart muscle, heart valves, blood vessels, soft tissues, etc., clinical symptoms include skin itching, bone pain, convulsions, fractures, etc., which affects the quality of life of dialysis patients. For clinical dialysis patients, the latest guidelines indicate that the blood phosphorus test value should be kept below 1.78mmol / L. Due to the influence of disease, hemodialysis patients mainly adopt the "3D" principle in the treatment of hyperphosphatemia: regular hemodialysis (dialysis), low-phosphorus diet (diet), treatment with phosphorus binders (drugs). Introduce the causes, symptoms and signs, hazards and related blood biochemical indicators of hyperphosphatemia to patients and their families, and list real cases to strengthen the degree of attention.

3. Aspects of Dietary Knowledge

For patients, diet control is one of the most difficult changes, while for HD patients, phosphorus control is the most difficult^[3]. After consulting a large number of documents, it is found that the dietary treatment of patients with HD and hyperphosphatemia is mainly through dietary education and intervention. Domestic food education is generally carried out by nurses, while abroad is implemented by nutritionists, nurses and pharmacists individually or jointly. Educating patients about diet should be based on the principle of balanced diet, low protein, low fat, and low phosphorus. Phosphorus mainly comes from food and is absorbed into the human body through the small intestine. Studies have shown that hyperphosphatemia may be related to eating habits^[4]. Factors affecting diet education include: gender, age, education level, occupation, body mass index, application of phosphorus binders, lack of communication between patients and medical staff, inadequate understanding of the consequences of poor blood phosphorus control, lack of understanding of the specific content of a low-phosphate diet, low compliance, complicated implementation of a low-phosphate diet, and concerns about increased risk of malnutrition.

(1) The style of dietary education mainly includes individualized education, such as the food exchange method^[5], intensive low-phosphorus diet management^[6], etc.; group education^[7,8]; behavior theory education, such as motivational interviews^[9], social cognitive theory^[10], etc.

(2) The place and content of diet education: it can include dialysis interval and concentration time education.

Our center mainly uses the quarterly Sunday or weekday morning time to concentrate on teaching, about 1 hour each time, high or low phosphorus content foods and techniques for reducing phosphorus intake, and issuing food phosphorus content inquiry cards, and keep a diet diary in a targeted manner. Use interactive education, in the process of guiding education, answer questions raised by patients in a timely manner. After each health education, he also asked questions on key issues, strengthened interactive links to check the acceptance of knowledge, and strengthened education on weak links.

4. Aspects of Drug Knowledge

Inform patients of the importance of taking medications, explain the names, therapeutic effects, dosage, methods of use, precautions and adverse reactions of commonly used phosphorus binders, instruct patients to take drugs on time and in amounts, and urge family members to supervise to improve patient compliance. Communicate with the doctor in charge in a timely manner and test in time to facilitate the adjustment of the medicine.

5. Aspects of Self-Management

Compliance status of maintenance hemodialysis patients: Kugler et al. found that^[11], many HD patients have poor self-management ability, and 80% of patients have poor diet and medication compliance. Although more and more patients are aware of the content of phosphorus in food, some research results have shown that^[12]: Many patients have difficulties in restricting phosphorus diet. The study of Morey et al.^[9] believes that this lifestyle change of phosphorus-restricted diet is very difficult and difficult to persist for a long time. The author even further pointed out that long-term dietary restrictions can easily lead to mild depression in patients. A questionnaire survey was conducted by medical staff in different countries on the observation of the dietary status of patients^[13]. It was found that patients' awareness of phosphorus gradually increased, but compliance was poor, and it was difficult to limit phosphorus. There are many reasons for the poor compliance of HD hyperphosphatemia patients, such as dependence on medical staff, lack of social support, uncertainty of disease, side effects of treatment, long-term treatment, complicated diet therapy and uncomplicated complications. Chan et al.^[14] believe that the factors that affect patient compliance are not only the patient's knowledge level, there are also age, dialysis time, education level, economic level, food preference, degree of lifestyle change, complicated diet preparation, forgetting, and side effects of behavior changes. Kugler^[11], zrinyi M^[15] and others found that the compliance of

female patients was significantly higher than that of male patients. Hollingdale et al.^[16] found that dialysis patients believe that it is difficult to implement a diet in the kidney in daily life. Patients should participate in the preparation of their diet plan to help patients overcome obstacles in order to improve compliance.

Nursing instruction is the teaching of disease treatment by professional nursing staff to patients, so that patients with hemodialysis and hyperphosphatemia can correctly understand the disease, know the cause and risk factors, and pay more attention, through face-to-face, multimedia lectures, brochures or diet cards, WeChat public accounts and interactive activities, the patient's cooperation with treatment and the quality of life of the dialysis interval are improved.

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Declaration

v Conflict of Interest

Examples of conflicts of interest include (but are not limited to):

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Supplementary figures, small tables, text etc.

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