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Postoperative Radiotherapy and N2 Non-small Cell Lung Cancer Prognosis: A Retrospective Study Based on Surveillance, Epidemiology, and End Results Database

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ABSTRACT

The purpose of this study is to clarify the significance of postoperative radiotherapy for N2 lung cancer. This study aimed to investigate the effect of postoperative radiotherapy on the survival and prognosis of patients with N2 lung cancer. Data from 12,000 patients with N2 lung cancer were extracted from the Surveillance, Epidemiology, and End Results database (2004-2012). Age at disease onset and 5-year survival rates were calculated. Survival curves were plotted using the Kaplan-Meier method. The univariate log-rank test was performed. Multivariate Cox regression were used to examine factors affecting survival. Patients' median age was 67 years (mean 66.46 ± 10.03). The 5-year survival rate was 12.55%. Univariate analysis revealed age, sex, pathology, and treatment regimen as factors affecting prognosis. In multivariate analysis, when compared to postoperative chemotherapy, postoperative chemo radiotherapy was better associated with survival benefits (hazard ratio [HR]= 0.85, 95% confidence interval [CI]: 0.813-0.898, P <0.001). Propensity score matching revealed that patients who had received postoperative chemo radiotherapy had a better prognosis than did patients who had received postoperative chemotherapy (HR=0.869, 95% CI: 0.817-0.925, P <0.001). Female patients and patients aged <65 years had a better prognosis than did their counterparts. Patients with adenocarcinoma had a better prognosis than did patients with squamous cell carcinoma. Moreover, prognosis worsened with increasing disease T stage. Patients who had received postoperative chemo radiotherapy had a better prognosis than did patients who had received postoperative chemotherapy. Postoperative radiotherapy was an independent prognostic factor in this patient group.

Keywords:Non-small cell lung cancer;Radiotherapy;Postoperative;Prognosis

1.Introduction

Lung cancer is a common cancer type and the leading cause of cancer-related deaths

worldwide [1]. In 2018, there were 2.1 million new lung cancer cases and 1.8 million lung cancer-related deaths, accounting for 18.4% of all cancer related deaths [2]. Non-small

cell lung cancer (NSCLC) accounts for about 85% of lung cancer cases [3], among which adenocarcinoma and squamous cell carcinoma are the predominant types. Surgery is the standard treatment for NSCLC. Currently there are no guidelines on adjuvant treatment for patients with postoperative pathological N2 disease stage. Adjuvant chemotherapy is the standard treatment for patients with positive lymph node metastasis after operation, but there was a significant difference in whether adjuvant radiotherapy was performed.

2.Methods

The Surveillance, Epidemiology, and End Results (SEER) database was examined for data from lung cancer patients with a pathological diagnosis of NSCLC confirmed during 2004-2012. (Figure 1). Patients were included in the present study if they met the following criteria: (1) Their postoperative stage was N2M0; (2) Squamous cell carcinoma or adenocarcinoma was confirmed by pathology testing; (3) Postoperative treatment involved chemotherapy alone; (4) Diagnosis was confirmed during 2004-2012.

Patients were excluded from the present study if they met any of the following criteria: (1) Unclear pathology results or confirmed diagnosis of a cancer type other than squamous cell carcinoma or adenocarcinoma; (2) Confirmed metastasis; (3) Intraoperative or preoperative treatment with radio-therapy; (4) No postoperative chemotherapy; (5) Confirmed multiple primary tumors; (6) Incomplete data.

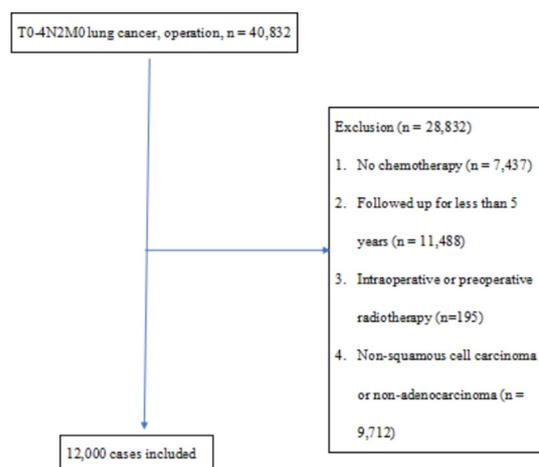


Figure 1. schematic illustration

Statistical analysis

IBM SPSS statistics version 25 was used for statistical analysis. Chi-square test was used to analyze categorical variables. Survival curves were plotted using the Kaplan-Meier method, and log-rank test was performed to analyze the differences in variables among groups. Differential variables were subjected to propensity score matching (PSM) in the postoperative chemoradiotherapy and postoperative chemotherapy group, and differences among groups were examined after matching. Univariate analysis was applied to compute models that included sex, stage, pathology, age, and treatment regimen. The variables that were significant in univariate analysis were included in multivariate analysis. Cox proportional hazards model was used for multivariate analysis. P-values <0.05 were considered statistically significant.

3.Results

Descriptive statistics

Among the 12,000 included patients. The age range was 19-95 years, with a median of 67

years (mean 66.46 ± 10.03 years). There 6127 cases (51.06%) were T0-2, 5873 cases (48.94%) were T3-4 (Table 1).

Table 1. Demographic and clinical characteristics of patients with squamous cell carcinoma and adenocarcinoma included in the Surveillance, Epidemiology, and End Results (SEER) database

Group	Cases	Percentage (%)
Sex		
Male	7119	59.33
Female	4881	40.67
Stage		
T0	66	0.55
T1	1640	13.67
T2	4421	36.84
T3	1842	15.35
T4	4031	33.59
Pathology		
Squamous cell carcinoma	6652	55.43
Adenocarcinoma	5348	44.57
Age		
≤ 65 years	5344	44.53
> 65 years	6656	55.47
Treatment		
Postoperative chemoradiotherapy	2606	21.72
Postoperative chemotherapy	9394	78.28

Univariate analysis

Kaplan-Meier curves were plotted according to sex, stage, pathology, age, and treatment regimen, revealing differences between groups. Women had a better prognosis than did men; patients aged 65 years and younger had a better prognosis than did patients older than 65 years; patients with adenocarcinoma had a better prognosis than did patients with squamous cell carcinoma; however, the prognosis worsened

with increasing T stage. The prognosis of patients who had received postoperative chemo radiotherapy was better than that of patients who had received postoperative chemotherapy. There were statistically significant differences in gender, stage, pathology, age and treatment plan between groups ($P < 0.01$) (Figure 2).

Multivariate analyses

Multivariate analyses are carried out on the variables with significance of univariate analysis. Gender, T stage, pathology, age and treatment were included in the multi-variate analysis. T stage was divided into Tt0-2 group and T3-4 group, as shown in Table 2.

Table 2. Univariate and multivariate analyses

Group	Univariate analysis			Multivariate analysis		
	P	OR	95% CI	P	HR	95% CI
Sex	< 0.001	1.434	1.236-1.663	< 0.001	1.131	1.085-1.178
Stage	< 0.001	0.722	0.654-0.796	< 0.001	0.820	0.788-0.854
Pathology	< 0.001	1.348	1.158-1.569	< 0.001	1.142	1.085-1.178
Age	< 0.001	0.808	0.697-0.933	< 0.001	0.887	0.852-0.923

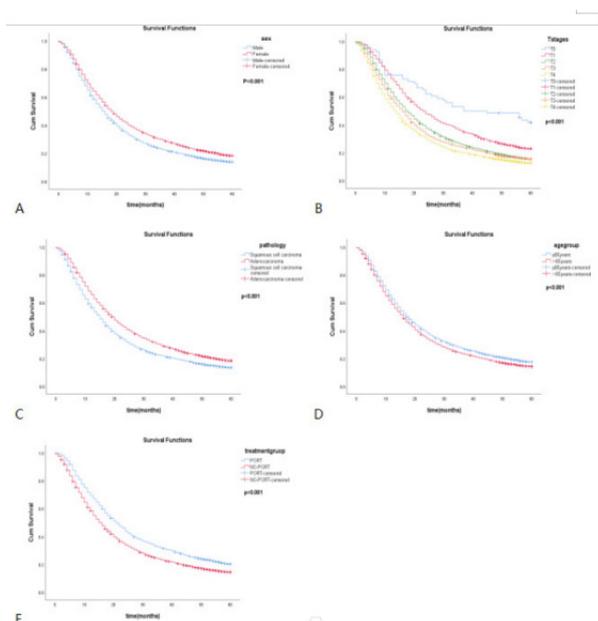


Figure 2. Kaplan-Meier curves of overall survival according to different groups. Survival difference of patients in group was statistically significant ($p < 0.001$).

Propensity score matching

After matching on sex, stage, pathology findings, and age, a total of 4,842 patients were included and divided evenly between the postoperative chemo radiotherapy (n=2421) and postoperative chemotherapy group (n = 2421). The sample included 2,779 men and 2,063 women in. There were 21 cases at T0 stage, 1,091 cases at T1 stage, 1,922 cases at T2 stage, 556 cases at T3 stage, and 1,252 cases at T4 stage. There were 2,185 cases of squamous cell carcinoma and 2,657 cases of adenocarcinoma. There were 2,300 patients aged 65 years or younger and 2,542 patients older than 65 years. The age range was 19-90 years, with a median of 66 years (mean 65.66 ± 9.72). The 5-year survival rate and median survival time before and after matching are presented in Table 2. Before matching, the median survival time was 17 months, and the 5-year survival rate was 12.55%; after matching, the median survival time was 19 months, and the 5-year survival rate was 18.5%. The prognosis of patients who had received postoperative chemo radiotherapy was significantly better than that of patients who had received post-operative chemotherapy alone (hazard ratio [HR]=0.869, 95% confidence interval [CI]: 0.817-0.925, $P < 0.001$). Treatment regimen was an independent prognostic factor for lung cancer patients (Table 3, and Figure 3 and 4).

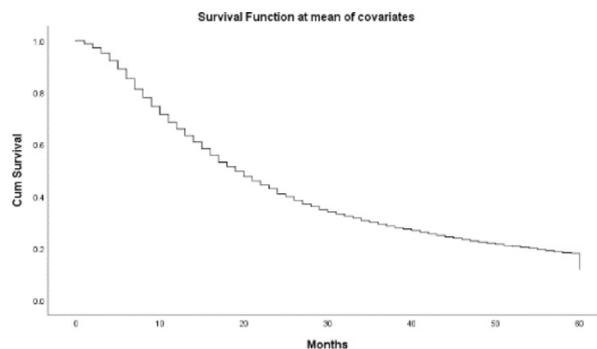


Figure 3. Survival curve at mean of covariates

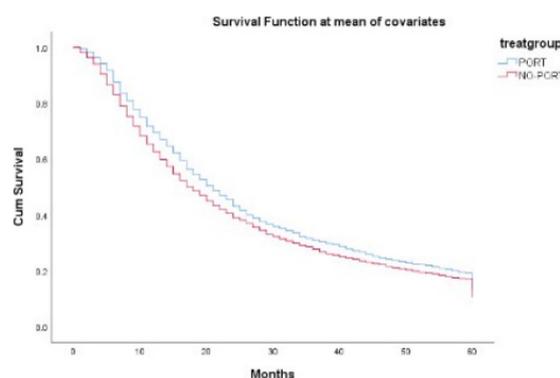


Figure 4. Significant difference survival curve of between after-matching PORT and NO-PORT ($p < 0.001$).

4. Discussion

NSCLC is a common type of lung cancer, of which adenocarcinoma and squamous cell carcinoma are the predominant subtypes. At the time of diagnosis, 30%-40% of patients have been reported to have disease at a locally advanced stage, accompanied by metastasis of cancer cells [4]. There are differences in the treatment of patients with N2 stage disease with mediastinal lymph node metastasis. Although comprehensive treatment is regarded as a standard regimen for N2 patients with resectable

NSCLC, the optimal combination therapy regimen remains unclear [5]. Chemotherapy is required to treat resectable NSCLC [6,7]. Treatment regimens include radical concurrent chemo radiotherapy, induction chemotherapy or chemo radiotherapy, and postoperative chemotherapy or chemo radiotherapy. It remains unclear which regimen is optimal, but 5-year survival rate for any regimen is 20-45% [8]. Moreover, 5-year overall survival rates associated with micro-single-station,

micro-multi-station, macro-single-station, and macromultistation involvement of mediastinal N2 lymph nodes have been reported as 34%, 11%, 8%, and 3%, respectively [9]. Surgery alone is insufficient, and the survival rate of patients with operable locally-advanced NSCLC is not high [10]. It is increasingly believed that patients with N2 disease stage should not be treated with surgery alone. In fact, evidence from randomized trials shows that adjuvant therapy is better than resection alone

Table 3. Survival outcomes for lung cancer patients included in the Surveillance, Epidemiology, and End Results (SEER) database, before and after propensity score matching

Group	Before matching				After matching			
	Cases	Percentage (%)	5-year survival rate (%)	Median survival time (months)	Cases	Percentage (%)	5-year survival rate (%)	Median survival time (months)
Sex								
Male	7119	59.33	11.14	16	2779	57.39	15.87	17
Female	4881	40.67	14.61	18	2063	42.61	22.06	22
Stage								
T0	66	0.55	30.30	37	21	0.43	38.10	28
T1	1640	13.67	19.02	23	1091	22.53	24.01	24
T2	4421	36.84	12.12	18	1922	39.69	18.21	20
T3	1842	15.35	12.87	16	556	11.48	16.19	11
T4	4031	33.59	9.95	14	1252	25.88	14.86	15
Pathology								
Squamous cell carcinoma	6652	55.43	10.34	15	2185	45.13	15.56	16
Adenocarcinoma	5348	44.57	15.30	19	2657	54.87	20.93	21
Age								
≤ 65 years	5344	44.53	14.20	17	2300	47.50	20.04	20
> 65 years	6656	55.47	11.22	16	2542	52.51	17.11	18
Treatment								
Postoperative chemotherapy + radiotherapy	2606	21.72	16.58	21	2421	50	20.12	21
Postoperative chemotherapy	9394	78.28	11.43	16	2421	50	16.89	17

[11,12]. The guidelines on NCCN (National Comprehensive Cancer Network) treatment recommend that adjuvant chemotherapy or adjuvant chemo radiotherapy be performed for patients with disease stage N2. The present study examined differences in survival rates between patients with pN2 disease stage treated with chemotherapy alone and chemo radiotherapy.

There is little controversy around postoperative chemotherapy as a standard postoperative treatment for N2 stage NSCLC with postoperative lymph node metastasis [13]. However, controversy surrounds administration of adjuvant radiotherapy. Based on data from the National Cancer Database (NCDB), Drake et al. have reported no difference in the median survival time between patients treated with adjuvant chemoradiotherapy and patients treated with adjuvant chemotherapy after R0 resection of disease at stage N0 and pathological N2 (3.9 years vs 3.8 years, $P = 0.705$) [14]. Moreover, Spicer et al. have conducted a retrospective analysis of data from four chest tumor centers, and compared 5-year overall survival (OS) and disease-free survival (DFS) in patients treated with N2 postoperative chemotherapy and N2 postoperative concurrent chemoradiotherapy. Their study revealed no differences in recurrence rates, recurrence mode, preoperative mortality, OS, or DFS in patients who had received preoperative invasive mediastinal staging [15].

It has been reported that postoperative radiotherapy can benefit pN2 patients. The American Thoracic Society guidelines did not support administration of adjuvant radiotherapy for occult N2 (NSCLC) after R0 resection. Postoperative radiotherapy increased the

local control rate but did not improve the OS rate [16]. A meta-analysis of relevant studies has shown that adjuvant radiotherapy lacked survival benefits after complete resection of NSCLC compared with operation alone. In 2006, Lally et al., using the SEER data, argued that postoperative radiotherapy improved the survival rate of N2 patients but did not benefit patients with disease stage N0 or N1 [17]. Douillard et al. have retrospectively analyzed data from pN2 patients who had received postoperative adjuvant radiotherapy, revealing that postoperative adjuvant radiotherapy generated more benefits but showed a negative effect on pN1 [18]. Based on data from the National Cancer Database, Herskovic et al. have conducted a stratified analysis to examine whether 2,691 patients with negative N2 (III A) resection margin who had received adjuvant chemotherapy during 2004-2013 should receive postoperative radiotherapy. In their study, the median survival time was 27.43 months and 25.86 months ($p < 0.05$), respectively. Postoperative radiotherapy significantly prolonged survival [19]. With improvements to radiotherapy technology, the local control rate increased, and treatment toxicity decreased [20]. Moreover, Su et al. have found that 1-year, 3-year, and 5-year OS rates associated with postoperative chemo radiotherapy and postoperative chemotherapy were 98.3% vs 86.1%, 71.7% vs 53.0% and 45.7% vs 39.0%, respectively ($P = 0.019$) [21].

In summary, there have been many studies aimed at examining the efficacy of N2 postoperative treatment regimens. In the present study, which involved analysis of data from the

SEER database, we have shown that age, sex, disease stage, pathology type, and treatment regimen are factors that affect the prognosis of patients with N2 lung cancer. In the present study, women and patients with adenocarcinoma had a better prognosis than did men and patients with squamous cell carcinoma. These findings suggest that targeted therapy can be considered to prolong survival. Multivariate analysis has revealed that survival associated with postoperative chemoradiotherapy was longer than survival time associated with postoperative chemotherapy alone. With the development of novel immunotherapy and targeted therapy regimens, further research is needed to identify the optimal postoperative treatment regimen for N2 lung cancer.

5. Conclusions

It can be seen from this study that the prognosis of N2 lung cancer is affected by many factors. Young, female and adenocarcinoma patients have more survival advantages. With the increase of T stage, the prognosis is worse and worse. Postoperative adjuvant radiotherapy is better than postoperative chemotherapy alone.

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Statement of Interest

There is no conflict of economic interests affecting its scientificity and credibility in this study.

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Research Progress on Effective Implementation of Whole Process Nursing Model for Patients with Cervical Cancer

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ABSTRACT

Cervical cancer has a high mortality rate in clinic. This disease seriously threatens the physical and mental health and life safety of patients. At present, radical surgery is mainly used for treatment, but in order to reduce the incidence of intraoperative and postoperative complications, corresponding nursing needs to be coordinated. This time focuses on the complications after radical surgery for cervical cancer, and puts forward the nursing methods of common complications of transabdominal radical surgery for cervical cancer. In order to improve the quality of nursing and life of patients, this paper summarizes the effective implementation of the whole process nursing model after cervical cancer surgery.

Keywords: Cervical cancer; Whole course nursing mode; Implementation

1. Introduction

Cervical cancer is a common gynecologic disease clinically, and it is a malignant tumor. The incidence rate of cancer in situ is 30~35 years old. The incidence of cervical cancer is increasing in 45~55 years old. With the change of living standard and lifestyle, the incidence of cervical cancer is increasing. Cervical cytology screening can detect and treat precancerous lesions and cervical cancer as early as possible, and reduce the incidence rate and mortality of cervical cancer. Surgery is suitable for the disease treatment needs of patients with early cervical cancer. It can completely remove the focus while preserving the patient's fertility. Affected by the disease and concerns about surgery, patients with cervical cancer will

have varying degrees of adverse emotions PJ, affecting the smooth progress of the operation and the expected aftereffects. Therefore, perioperative nursing intervention is very important. This aspect needs in-depth study and continuous analysis.

2. Radical Operation of Cervical Cancer

Cervical cancer is the second most common tumor in women. Combined with the statistical treatment of the International Cancer Research Center under who, it can be effectively obtained [1]. At present, the vast majority of new cases of cervical cancer in the world every year are in developing countries, which occupies the first place of malignant tumors of female reproductive system in China [2]. U.S. surgeons rapidly shifted from minimally invasive to open

hysterectomy for cervical cancer. Decreasing utilization of minimally invasive surgery was associated with an increase in perioperative complications and longer hospital [3]. Wang Zhi [4] thinks postoperative cervical cancer is easy to affect the quality of life of patients. Improving or preventing postoperative vaginal contracture has a positive impact on patients' life, which can effectively improve the safety, effectiveness and safety of patients' treatment, and promote the satisfaction of patients with cervical cancer. It also fully shows that this method can be widely used in clinic and improve the quality of life of patients with cervical cancer after operation. Yang Fan Chun's [5] research shows that cervical cancer surgery has a history of more than 100 years, from open surgery to minimally invasive surgery (MIS). Since the era of clinical exploration and practice, minimally invasive gynecological surgeons have been exploring new frontiers in the field of gynecological surgery. Compared with laparotomy, the postoperative complications of cervical cancer surgery are relatively small. The main focus is on reducing the incidence rate and duration of hospitalization. This is also an important method for treating early cervical cancer. In 2018, the clinical research article on cervical cancer surgery published in the New England Journal of medicine clearly made laparoscopic surgery for early cervical cancer subject to more rigorous review and negative views. Most studies have begun to explore the concept of standardized surgery for early cervical cancer. When outlining the standardized characteristics of cervical cancer surgery. The current situation of cervical cancer surgery was analyzed to improve the

surgical treatment of cervical cancer.

Patients with cervical cancer surgery will worry that the surgery will cause the loss of female characteristics, sexual function and fertility, will be despised and abandoned by their husbands, friends and society, will also be more afraid of losing their position due to illness, fear of losing their economic source, and are more likely to have psychological problems such as anxiety, depression and fatigue after surgical treatment. Anxiety in patients undergoing cervical cancer surgery is a common phenomenon, and the important reason for anxiety is the fear that poor recovery will affect their future sexual life and easy aging. It is concluded that most patients' understanding of cervical cancer surgery is not correct, which is also an important reason for patients' anxiety. Sexual dysfunction is common in postoperative patients with cervical cancer. The quality of sexual life is one of the important contents to evaluate the quality of life of patients with cervical cancer. This is mainly because the fear of tumor makes the mental pressure too heavy and it is difficult to have sexual interest. Therefore, psychological disorder is an important reason to affect the quality of sexual life of postoperative patients with cervical cancer. Pelvic floor dysfunction and ovarian endocrine function decline caused by cervical cancer surgery are also important factors affecting the quality of life of patients.

Most important factors affecting the quality of life of cancer patients involve family support, and better social and family support is more conducive to cancer patients to obtain better quality of life and psychological state, The

spouses of some cervical cancer patients are very important elements of social and family support. The spouse's attitude and wrong understanding, such as some spouses think that their wife loses sexual function after operation, worry that the tumor is infectious, etc., have significantly reduced the couple's quality of sexual life. Some studies have also shown that family factors are significantly related to patients' emotional disorders, and even the risk of emotional disorders can be determined by evaluating the degree of family harmony. The quality of life of cervical cancer patients is affected by many factors. Due to various reasons, such as poor postoperative incision healing, disease control, physical weakness. After treatment, complications, chemotherapy and other factors can affect their quality of life. The characteristics of patients will also have an impact on the quality of life. Therefore, we need to pay attention to the nursing situation of patients after surgical treatment, and pay attention to the analysis of the implementation and specific development direction of the whole process nursing model in the nursing of patients with cervical cancer after surgery.

In clinical practice, total hysterectomy, sub extensive total hysterectomy and pelvic lymph node dissection, extensive total hysterectomy and pelvic lymph node dissection are generally used to treat patients, and the appropriate operation methods are selected according to whether the patients have the requirements of preserving reproductive function and different stages. The operation will cause physical and psychological stress reactions to the patients. Therefore, it is necessary to implement active

nursing intervention to enable patients to recover as soon as possible. After the implementation of surgical treatment of cervical cancer, the nursing of vital signs monitoring and diet nursing for patients is an important part of traditional nursing for cervical cancer surgery. The prognosis of patients can be effectively improved to a certain extent, but traditional nursing has mechanical and limitations to a certain extent. Nurses implement nursing operations according to the doctor's instructions. It can not find and deal with complications in time, resulting in high incidence of complications and poor prognosis. Therefore, choosing a more comprehensive, overall and detailed nursing model is very important to improve the quality of life of patients with cervical cancer.

3.Effective Implementation Path of Whole Process Nursing Model for Patients with Cervical Cancer

The condition of cervical cancer disease is complex and the psychological burden of patients is heavy. Poor cooperation will affect the treatment effect. Therefore, it is particularly important to carry out effective nursing intervention for patients. The whole process nursing intervention can be applied to the treatment of cervical cancer patients, alleviate the tension of patients, enable patients to cooperate more actively with the treatment and significantly improve the treatment effect. At the same time, through the explanation of nursing staff, the patients can master the basic knowledge and precautions of the disease and speed up the recovery of the disease. The whole process nursing intervention has important

clinical application value for the treatment of cervical cancer. It can alleviate the anxiety of patients, improve the nursing satisfaction of patients, significantly shorten the length of hospital stay, reduce the hospitalization cost, significantly improve the treatment effect and promote the recovery of patients.

Binggang Ye [6] thinks holistic health care includes the prevention and treatment of diseases and the regulation of sub-health status. On the basis of whole course nursing, it can promote blood circulation and regulate various physiological parameters, which has an overall effect in overall health nursing. Duan Xia [7] think nursing quality evaluation is an important part of medical quality management. It is of great practical significance and research value for nursing supervisors to understand the shortcomings in the process of nursing quality evaluation and then improve the overall nursing quality. Data were collected through in-depth interviews and analyzed by content analysis. It is of great practical significance to further improve the evaluation standard of nursing quality, modify the evaluation content guided by the needs of patients, use scientific evaluation methods to evaluate the nursing quality, and scientifically and reasonably compare the nursing quality between hospitals, as well as the longitudinal comparison of hospital nursing quality. These methods can enhance the core competitiveness of the hospital and benefit more patients.

3.1 High Quality Psychological Care

The nursing staff should actively communicate with the patients and the language should be easy to understand. They should

always listen to the patients' ideas, timely dredge the patients' bad emotions, selectively use music therapy to relieve the patients' emotions, actively share successful cases with the patients, help the patients establish the confidence to overcome the disease, and can effectively relieve the patients, So that patients can actively cooperate in postoperative rehabilitation, which has a positive impact on the early recovery of patients. Guifeng Xue [8] to analyze and comprehensively study the clinical effect of humanized psychological nursing model in general surgery nursing. The subjects were randomly divided into study group and control group. Number of samples in each group $n = 100$. Patients in the control group received routine general surgery nursing plan, while patients in the study group received the same nursing plan, but added humanized psychological nursing mode. The two groups of indicators were compared and analyzed. There was significant difference in patients' satisfaction with nursing service ($P < 0.05$). It can fully show that the implementation effect of humanized psychological nursing model in general surgery nursing is remarkable, and the patients' psychological state and satisfaction with nursing services have been improved. Therefore, it is worthy of clinical application and further promotion.

Redondo Elvira Tamara [9] review and analyze the most influential variables for patients to achieve their mental health level, verify that spirit, resilience and social support are the basic pillars of mental health construction and have an impact on patients' disease rehabilitation, clearly use the terms of mental well-being, discomfort

and quality of life to replace mental well-being, and There is a certain consensus on whether spiritual and social support are predictors of psychological well-being. In the process of effective disease treatment, the resilience, social support and spirit of patients are highly related variables at the end of life, which plays a decisive role in mental health.

Lingens Solveigh P [10] Relevant studies believe that it can provide important psychological care for cancer patients and have an important impact on patients' disease treatment. However, if we can pay attention to the impact of disease treatment on fatigue, we can better determine the fatigue track during psychological care, check the factors that distinguish these tracks, and predict the fatigue severity of patients after psychological care. In potential class growth analysis, repeated measurement analysis and linear regression analysis. It can be concluded that the fatigue of patients after surgical treatment is statistically significantly reduced, but this reduction has nothing to do with clinical practice. RMA showed that fatigue trajectory time had a major impact on depression, anxiety, personal control and disease cognition. The severity of fatigue and physical symptoms at T1, rather than demographic or clinical factors, can predict the severity of fatigue at T3. Cooperating with the psychological nursing model during the patient's tumor treatment can alleviate the symptoms of fatigue, depression, anxiety and physical symptoms. Therefore, it is necessary to strengthen the implementation of fatigue treatment for patients.

3.2 Postoperative Nursing Intervention

Observe the postoperative reaction of patients and treat them in time according to the doctor's advice. Relevant health education was carried out after operation. Attention should be paid to patients' subjective feelings, timely intervention of dry mouth and pain after operation, using mume spray to solve the problem of dry mouth, and developing corresponding pain relief methods. The nursing staff recorded the patient's heart rate and average artery every 15 - 30 minutes. Blood pressure and blood oxygen saturation. After the patient's vital signs are stable, it can be recorded every 4 hours. The whole nursing staff used intermittent clamping catheter to train the bladder function of patients, so as to better promote the faster recovery of micturition function. After the patient's physical condition improves, the nursing staff can guide the patient to effectively carry out limb function recovery training, so as to promote the recovery of limb function and prevent the complications of disuse syndrome.

3.3 Ward Nursing

Carry out nursing intervention on the ward where the patient is located to keep the ward ventilated, clean and comfortable. Jacqueline Peet RN [11] believes that understanding and creatively involving nurses in potential ward management is a prerequisite for forming more safe and effective hospital nursing. Therefore, according to the practical research results, promoting front-line nurses and teams to develop a people-centered workplace is the key to sustainable improvement of patient safety.

3.4 Diet Care

Formulate corresponding diet for patients, focusing on balanced nutrition and easy

digestion. Follow up the patient's eating situation in each shift and adjust the patient's diet plan in time. Papadimitriou Nikos [12] shows that diet and nutrition are modifiable risk factors for several cancers, but due to the inherent bias, the association between the two may be defective, and the patient's disease recovery also largely depends on a single assessment of diet using the food frequency questionnaire. We conducted a comprehensive review of the meta-analysis of observational studies, focusing on the strength and effectiveness of the evidence for the association between food / nutrient intake and 1 patient's cancer treatment and risk of death.

3.5 Develop Continuous Care Plan

After the surgical treatment of cervical cancer patients, when the patients are discharged from the hospital, they need to issue relevant health prescriptions to help the patients understand the precautions for disease recovery, and follow up the patients on time in combination with Wechat and telephone, so as to follow up the patients' diet, the degree of cooperation and relevant contents in patients' rehabilitation exercise and follow-up. Patients are encouraged to normally participate in the process of social interaction, so as to avoid adverse emotions such as inferiority complex, so that the postoperative rehabilitation process of patients will not be adversely affected by emotions.

4. Conclusions

The surgical treatment of cervical cancer, i.e. extensive hysterectomy and pelvic lymph node dissection, is relatively common in the treatment of early cervical cancer. The advantage

of this operation is that it can implement individualized and standardized treatment, better preserve the ovarian endocrine function, and is not easy to affect the vaginal function. However, when performing transabdominal cervical cancer surgery, patients will also be more prone to urinary retention and urinary tract infections. Based on this, we should take corresponding nursing measures to reduce the incidence of complications. At this stage, according to the continuous renewal and enrichment of medical concepts, the whole process high-quality nursing method is fully applied to the nursing of cervical cancer patients. This method is a nursing method that can make corresponding intervention according to the physiological, social and emotional needs of patients. Based on the "people-oriented" concept, through high-quality nursing in preoperative, intraoperative and postoperative stages, It is effective to adjust patients' bad psychological state, improve patients' treatment safety, promote patients' compliance behavior, and improve patients' quality of life. With its comprehensive and scientific nursing method, the whole process nursing measures can comprehensively improve the quality of life of cervical cancer patients and effectively improve the treatment compliance. It has high clinical value and is worth popularizing.

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Discussion on Nursing Mode of Ecmo in Treating Severe Patients

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ABSTRACT

Objective: To evaluate the nursing effect of Ecmo treatment for severe patients. **Methods:** 66 patients treated with extracorporeal membrane pulmonary oxygenation were included in the experimental data. From August 2018 to August 2019, the patients were divided into experimental group and reference group by random digital table method, each group was 33 cases. Routine nursing and targeted nursing were performed to compare the complications of the two groups. **Results:** (1) The correlation index of extracorporeal membrane pulmonary oxygenation treatment before treatment was consistent, $P>0.05$, the oxygen saturation and oxygen partial pressure of 2h, 4h after treatment in the experimental group were higher than those in the reference group, compared with the reference group, the carbon dioxide partial pressure of 2 h, 4 h after treatment in the experimental group was lower, showing statistical significance of data test ($PP>0.05$). (2) The incidence of infection, bleeding, coagulation, embolism and hypotension in the experimental group (12.12%) was lower than that in the reference group (45.45%), showing statistical significance ($P<0.05$). **Conclusions:** the specific nursing effect of extracorporeal membrane pulmonary oxygenation in severe patients can effectively improve the success rate of treatment, and the possibility of complications during treatment is low.

Keywords: Extracorporeal membrane oxygenation; Ecmo; Critical; Nursing

1. Introduction

Extracorporeal membrane pulmonary oxygenation (Extracorporeal Membrane Oxygenation, ECMO) is an important guarantee of cardiopulmonary failure cardio-pulmonary bypass. It is a continuous life support therapy assistant technique. The venous blood of the patient is extracted from the body through the catheter and transported back to the patient's body through the action of artificial lung and artificial heart. During the course of extracorporeal membrane oxygenation

treatment, the nursing work has been required. In this study, the nursing measures of extracorporeal membrane oxygenation for severe patients were analyzed and the application effect of targeted nursing was discussed.

2. Clinical Data and Methods

2.1 Clinical Information

For the treatment of severe patients with extracorporeal membrane pulmonary oxygenation from August 2018 to August 2019, 66 cases. The grouping method is the random

number table method. They were experimental group (n=33) and reference group (n=33). In the experimental group, the ratio of severe female to male was 22 to 11, up to 68 years. The age limit is 38, and age mean was (43.29±13.78) years. Mechanical ventilation time longest 5 d, mechanical ventilation time shortest 2 d, mechanical ventilation time mean (3.59±0.58) d. In the reference group, the ratio of severe female to male was 20 to 13. Age limit 68 years old, age limit 37 years old, age average is (43.25±13.76) years old. 6 d, maximum mechanical ventilation 2 d, minimum mechanical ventilation mean mechanical ventilation time was (3.62±0.60) d. To verify the data of age, sex and mechanical ventilation time in 2 groups of patients treated with extracorporeal membrane oxygenation, P>0.05, Comparable characteristics. Inclusion criteria: (1) All patients were severe pneumonia patients; (2) The patients could not correct hypoxemia after mechanical ventilation; (3) Patients or family members are aware of this study, Voluntary participation. Exclusion criteria: (1) malignant tumor patients; (2) Patients with mental illness.

2.2 Method

According to the routine nursing, the Bio line coated artery, vein intubation and extracorporeal membrane pulmonary oxygenation package were used to treat the femoral vein, centrifugal pump, oxygenation instrument and jugular vein. The flow rate of extracorporeal membrane oxygenation instrument is 2.5-4.2 L/min, the average operating time is 219 h, the oxygen concentration is adjusted to 30-40, the positive pressure at the end of respiration is 4-5 cmH, and the operating

time is 21920, moisture volume adjusted to 5-6 ml/kg. 4 h Prothrombin time and arterial blood gas were tested h to ensure nursing care during extracorporeal membrane pulmonary oxygenation. Experimental group to carry out targeted nursing, specific measures include: first, vital signs monitoring, extracorporeal membrane pulmonary oxygenation treatment of severe patients vital signs monitoring, Keep the heart rate at 80 beats / min, to evaluate the blood pressure level and give the patient drugs to control blood pressure. For some patients with excessive respiratory frequency, the problem of blood oxygen saturation should be prevented, and the actual situation of patients should be given drug treatment. The arterial pressure level of the patients should be dynamically monitored, especially during the adjustment of the patient's posture, and the pressure sensor system should be protected. Every 2 h the pupil of the patient was observed to prevent intracranial hemorrhage caused by heparin. Every 2 h the patient's body temperature level is monitored to prevent the patient from hypothermia. Hypothermia will cause abnormal hemodynamic indexes and affect the patient's life safety. If the patient's conditions permit, the rectal temperature is detected and maintained at 35-36 degrees. Second, airway nursing, during sputum suction operation, should be strictly in accordance with the requirements of aseptic operation, as far as possible to implement shallow attraction, to prevent injury to patients' airway mucosa. The patient's airbag pressure is checked every 12 h and maintained at cmH 25-3020, give the patient heating, humidification management to ensure its airway mucosal humidification effect.

Third, hemagglutination index monitoring, during extracorporeal membrane pulmonary oxygenation treatment, patients are more likely to develop thrombus, so during the treatment of patients will be systemic heparinization, but during the treatment is very likely to occur excessive anticoagulant problem, this should be targeted at the patient's partial coagulation time monitoring, maintain its partial coagulation time of 150-200s, platelet maintenance at $100 \times 10^9/L$ above, observe the skin, mucous membrane, arteriovenous puncture position, drainage fluid, once bleeding, subcutaneous bleeding or blood substances, the patient should be informed in time to adjust the amount of heparin.

2.3 Observation Indicators

Blood oxygen saturation, oxygen partial pressure and carbon dioxide partial pressure were monitored 2h, 4h severe patients before and after treatment. The complications of extracorporeal membrane pulmonary oxygenation in severe patients were recorded, including infection, bleeding, coagulation, embolism, hypotension and so on.

2.4 Statistical Analysis

The data of all 66 cases of severe patients treated with extracorporeal membrane pulmonary oxygenation were expressed as (mean \pm standard deviation) in SPSS 19.0 software,

including: oxygen saturation, oxygen partial pressure, carbon dioxide partial pressure index before and after treatment, t test was carried out to meet the normal distribution. The counting data is expressed in the form n(%) cases, and the data is X²Test, including: extracorporeal membrane oxygenation treatment of severe patients with infection, bleeding, coagulation, embolism, hypotension and other complications. $P < 0.05$, showing statistical significance of data test.

3. Results

Comparison of oxygen saturation, oxygen partial pressure and carbon dioxide partial pressure between the 2 h, 4 h before and after treatment of severe patients with extracorporeal membrane oxygenation $P > 0.05$, the blood oxygen saturation and oxygen partial pressure in the experimental group were higher than those in the reference group. Compared with the reference group, the carbon dioxide partial pressure 2h, 4h the experimental group was lower after treatment ($P > 0.05$).

Comparison of complications such as infection, bleeding, coagulation, embolism and hypotension in severe patients treated with extracorporeal membrane oxygenation.

Table 1. Comparison of blood oxygen saturation, partial pressure of oxygen and partial pressure of carbon dioxide 2h, 4h before and after treatment of severe patients with extracorporeal membrane oxygenation

Group	Cases (n)	(% blood oxygen saturation)			Oxygen partial pressure (mmHg)			Carbon dioxide partial pressure (mmHg)		
		Pre-treatment	2 h after treatment	4 h after treatment	Pre-treatment	2 h after treatment	4 h after treatment	Pre-treatment	2 h after treatment	4 h after treatment
Experimental group	33	73.60±1.67	93.46±3.40	96.66±2.35	43.87±5.26	65.80±1.31	81.40±1.41	47.49±3.86	43.46±1.18	40.57±2.19
Reference groups	33	73.58±1.62	88.21±3.08	92.37±3.48	43.90±5.23	58.76±3.49	70.61±2.57	47.52±3.88	45.93±2.14	43.09±3.63
t		0.0493	6.5739	5.8688	0.0232	10.8487	21.1449	0.0314	5.8062	3.4146
P		0.9607	0.0000	0.0000	0.9815	0.0000	0.0000	0.9749	0.0000	0.0011

Table 2. Comparison of complications such as infection, bleeding, coagulation, embolism and hypotension in patients with severe n(%) by extracorporeal membrane oxygenation

Group	Cases (n)	Infection	Bleeding	Blood clotting	Embolism	Low blood pressure	Total complications
Experimental group	33	2 (6.06)	1 (3.03)	0 (0.00)	0 (0) .00	1 (3.03)	4 (12.12)
Reference groups	33	4 (12.12)	4 (12.12)	2 (6.06)	2 (6.06)	3 (9.09)	15 (45.45)
X 2							8.9428
P							0.0027

Compared with the complications of extracorporeal membrane pulmonary oxygenation in severe patients (see Table 2), the incidence of infection, bleeding, coagulation, embolism and hypotension in the experimental group (12.12%) was lower than that in the reference group (45.45%), showing statistical significance of data test ($P < 0.05$).

4. Discussion

Extracorporeal membrane pulmonary oxygenation is the current advanced treatment of cardiopulmonary diseases, which can be divided into two forms. One is to carry out oxygenation after venous blood is induced, then to the vein, and generally to treat respiratory failure. The other is to oxygenate venous blood and return to

the artery. The results showed that the incidence of complications such as infection, bleeding, coagulation, embolism and hypotension in the experimental group 2h, 4h lower than that in the reference group. During the treatment of extracorporeal membrane pulmonary oxygenation, nursing staff should strictly abide by the principle of aseptic operation to prevent infection during the further period. Most of the patients treated by extracorporeal membrane pulmonary oxygenation are critical and critical. There are relatively many invasive pipelines, the immune system function of patients is seriously decreased, and the proportion of infection is high. Therefore, the requirement of clinical nursing is very high, nursing staff should strictly abide by the aseptic operation during the

implementation of targeted nursing, and carry out nursing work in the aseptic state. If there is blood stains and sweat, it should be cleared to avoid the upward transmission of bacteria. In addition, for some patients who already have infection, we should apply blood culture, make clear the pathogenic bacteria of the patients, and give their targeted antiinfection treatment to ensure the safety of the patients. At the same time, the coagulation time of the patients should be monitored in nursing work, and the amount of heparin pump should be adjusted according to the actual situation of the patients. If the patients already have bleeding tendency, they should find out the cause immediately. And inform the doctor to deal with the problem of intracranial hemorrhage.

Combined with the above results, this study has obvious effect on the treatment of severe patients with extracorporeal membrane pulmonary oxygenation, and the blood gas related indexes of the patients have been significantly improved, and the incidence of complications during the treatment of patients has been reduced. Targeted nursing in extracorporeal membrane pulmonary oxygenation treatment has clinical value.

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Effects of Probiotics on Gut Microbiota in Type 2 Diabetes Patients

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ABSTRACT

Objective: To study the effect of probiotics on gut microbiota **Methods:** Select Type 2 diabetes patients to take orally probiotics for 24 weeks, collect stool samples of subjects at the baseline and end of the trial, identify and analyze gut microbiota of each sample by 16srRNA high-throughput sequencing, and compare the changes of blood glucose, blood lipid and insulin resistance before and after the intervention. **Results:** A total of 75 patients completed clinical observations. 16srRNA high-throughput sequencing showed that the proportion of the subjects with increased Actinobacteria and Tenericutes at the end of the trial has increased (37.8% and 75.7% respectively). The genus level analysis showed that the number of subjects with increased intestinal probiotics and with decreased conditioned pathogens all increased. Cluster analysis before and after intervention showed that the gut microbiota of samples in the same group had a higher similarity. Compared with the subjects at the baseline status, at the end of the trial after the intervention, fasting blood glucose (FBG) of the subjects significantly decreased ($P<0.05$), the proportion of the subjects with triglyceride (TG) and cholesterol up to standard increased, and HOMAIR was significantly improved ($P<0.05$). **Conclusions:** Probiotics can regulate the gut microbiota of Type 2 diabetes patients, promote fasting blood glucose (FBG) to reach the standard and improve insulin resistance, and help improve lipid metabolism.

Keywords: Probiotics; Type 2 diabetes ;Insulin resistance ;Gut microbiota

1.Introduction

In recent years, the relationship between gut microbiota and Type 2 diabetes has attracted more and more attention from scholars both at home and abroad [1]. The changes of gut microbiota are closely related to insulin resistance, obesity, systemic inflammation and oxidative stress of the host [2]. Gut microbiota imbalance increases insulin resistance and thus affects the progress of glucose metabolism and

its complications. This study is aimed to study the changes of gut microbiota in Type 2 diabetes patients by probiotics intervention and explore the clinical application value of this intervention method.

2.Materials and Methods

2.1Research Objects

101 Type 2 diabetes patients who received treatment from the Department

of Endocrinology and Metabolism, China-Japan Union Hospital of Jilin University from January 2017 to July 2017 were selected as subjects, meeting the requirements of $7.0\% \leq \text{HbA1c} \leq 10.0\%$, with the history of diabetes for one week to 26 years. All subjects were informed of the research plan and then participated in the trial, voluntarily followed the guidance of the researchers and signed informed consent. Exclusion criteria: patients with severe impairment of liver and kidney functions, heart failure, fever, infection, or acute diabetic complications, pregnant and lactating women, or patients with FBG no less than 13.3 mmol/L, or patients with severe hypertension (systolic blood pressure no less than 180mmHg and/or diastolic blood pressure no less than 110 mmHg) or patients researchers considered inappropriate for the trial. The diagnosis of Type 2 diabetes conforms to the diagnostic criteria of WHO diabetes formulated in 1999.

2.2 Research Plan

A special person is responsible to collect the information of the medical history of all subjects, and record their gender, age, course of diseases, height, weight and blood pressure. Require the subjects to have a regular diet and guide them to take the similar daily exercise, and on the basis of keeping the same hypoglycemic treatment plan unchanged, probiotics products were taken daily, including three Changle capsules taken orally three times a day and one bag of Jiangtangqi granule taken two times a day after mixing with water 1.5 hours before meals (all produced by Jilin Tiansanqi Pharmaceutical Co., Ltd.) for 24 weeks. Changle capsule is a health food mainly made from corn flour,

rice flour, defatted milk powder, wheat flour, defatted soybean flour, Isomaltooligosaccharide, sugar, glucose and yeast extracts. It contains 1.2×10^8 CFU Bifidobacterium bifidum, 4.2×10^8 CFU Lactobacillus acidophilus, and 4.3×10^8 CFU Streptococcus thermophilus per 100g. The effective ingredients of Jiangtangqi granule are soybean flour, milk powder, cocoa powder, calcium powder, yam flour, konjac flour, spirulina powder, almond powder, Fructus Mume powder, licorice powder, etc. Take it before meals to increase the sense of satiety and the carbohydrates in it play a role similar to prebiotics. During the trial period, all subjects continued the original hypoglycemic, hypotensive, hypocholesterolemic treatment plan. A total of 101 subjects participated in the trial, the clinical observation of 75 subjects was completed and these subjects were safely discharged.

2.3 Testing Indicators

FBG, and blood glucose, blood lipid, liver function, kidney function, urine routine, fasting C-peptide (FCP), glycosylated hemoglobin (HbA1c) and other indicators 2 hours after meals of each subject were detected at the baseline and end of the trial. The feces of the subjects at the baseline and end of the trial were collected for 16srRNA high-throughput sequencing of gut microbiota (implemented by Shanghai Omicspace Biotech CO., LTD) to identify and analyze the intestinal microbial diversity of the samples. $\text{HOMAIR} = (\text{FCP} \times \text{FBG}) / 22.5$.

2.4 Statistical Methods

The data in normal distribution were expressed by means \pm standard deviation (SD) and analyzed by paired t-test. The data in non-

normal distribution were expressed by median (quartile) and analyzed by paired rank sum test. All data were analyzed by SPSS software.

3.Results

The clinical observation of 75 patients on the effect of the joint intervention on the general condition, blood glucose, blood lipid and insulin resistance of subjects was completed (with an average age of 56.5 ± 7.5 years), including 25 male and 50 female patients. The body weight, systolic and diastolic blood pressure of the subjects decreased at the end of the trial compared with those at baseline, but there was no statistical significance. The fasting blood glucose (FBG) significantly decreased, and the difference was statistically significant ($P < 0.05$). The blood glucose and glycosylated hemoglobin decreased 2 hours after meals, but there was no statistical significance (Table 1). HbA1c $< 7.0\%$ was defined as reaching the standard, and the HbA1c standard-reaching rate of subjects was 27.7% when the subject entered the group and 35.6% when the subject left the group. The effect of the joint intervention on blood lipid was not statistically significant (Table 1). Triglyceride (TG) < 1.7 mmol/L was defined as reaching the standard, the triglyceride standard-reaching rate was 38.6% when the subject entered the group and 52.5% when the subject left the group. The total cholesterol (TC) < 5.2 mmol/L was defined as reaching the standard. The TC standard-reaching rate was 44.6% when the subject entered the group and 61.4% when the subject left the group. There was no statistical difference in fasting C-peptide (FCP) level between the subjects before and after the

intervention. HOMAIR was used to represent the insulin resistance level. HOMAIR of the subjects decreased at the end of the trial after the intervention, the difference was statistically significant ($P < 0.05$), and insulin resistance was improved.

Safety

During the visit, no severe hypoglycemia and cardiovascular and cerebrovascular diseases occurred in all subjects, and there was no significant change in liver function and renal function of all subjects before and after the joint intervention.

Results of gut microbiota sequencing

After the feces of all subjects were collected, the DNA sample and OUT generation were all completed by the sequencing company. A total of 70 effective samples were obtained, with "pre-" representing preintervention samples and "post-" representing post-intervention samples. a: The analysis of Alpha diversity is obtained by statistical software. The Chao index represents the abundance of flora, and the Shannon index represents the diversity of flora. The OUTs dilution curves of each sample are shown in Figure 1 and the Shannon dilution curves are shown in Figure 2. The curves with different colors represent different samples. With the increase of sequencing quantity, the dilution curves of each sample gradually become flat, indicating that the samples have sufficient test depth, rich species, and enough sequencing quantity to reflect the microbial information in the samples. The Runk-Abundance curve of each sample is shown in Figure 3. With the increase of the number of flora in each sample, the species abundance of each sample decreases.

When the species abundance is lower than $1e-04$, the curve is close to a plateau, and the genus of most samples is between 100 and 200. b: flora structure and cluster analysis. The flora structures of all samples at the phylum level are shown in Figure 3 and among them, Firmicutes, Bacteroidetes and Proteobacteria accounted for a higher proportion in each sample, and all of them are the dominant flora. Tenericutes accounted for a higher proportion in a total of 22 samples, including 8 samples (24.2%) in the pre-group and 14 samples (37.8%) in the post-group. Actinobacteria accounted for a higher proportion in a total of 32 samples, including 4 samples (12.1%) in the pre-group and 28 samples (75.7%) in the post-group. Cyanobacteria accounted for a slightly higher proportion in a total of 5 samples including two samples in the pre-group and three samples in the post-group. The above results showed that after the intervention, the proportion of flora in each sample changed and the abundance of Actinobacteria and Tenericutes increased. Cluster analysis showed that the pre-group represented the baseline status and the post-group represented the status at the end of

trial, and the overall performance was that the samples in the pre-group and the samples in the post-group clustered first in the group. and the 9 samples in the post-group clustered together at the top of the tree diagram of phylum level similarity analysis shown in Figure 3, followed by 7 and 8 samples in the pre-group clustered and merged, indicating that the gut microbiota of the samples in the same group has high similarity. In the overall tree diagram, there was a crossed and clustered position between the pre-group and post-group, which is related to the complexity of gut microbiota in patients with diabetes and relatively many confounding factors. c: Genus level analysis showed that compared with the baseline status, the number of the subjects with increased intestinal probiotics and with decreased conditional pathogens all increased at the end of the trial. The subjects with increased Bifidobacterium under Actinobacteria in probiotics accounted for 62.2%. The subjects with increased L.Lactobacillus in Lactobacillus under Firmicutes increased by 21.6%. In terms of the conditional pathogens, the subjects with decreased Escherichia coli under Escherichia

Table 1. Effect of joint intervention on the subjects' blood glucose, blood lipid and insulin resistance

	Baseline	End of trial	t	P
FBG (mmol/L)	10.36±3.63	7.81±3.15*	6.68	<0.001
Blood glucose 2h after meals(mmol/L)	18.12±6.35	17.35±5.22	1.02	0.31
HbA1c (%)	8.14±2.47	7.82±1.46	1.21	0.23
TC (mmol/L)	5.38±1.27	5.27±1.16	0.99	0.33
TG (mmol/L)	1.86 (1.15, 2.87)	2.00 (1.30, 2.80)	-0.91	0.37
FCP (ng/ml)	1.25±0.75	1.10±0.68	1.15	0.26
HOMA-IR	0.68±0.21	0.55±0.17*	3.45	0.03

*P<0.05

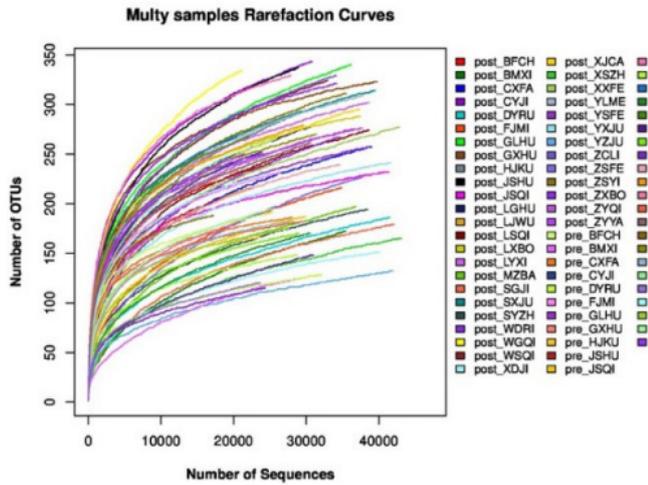


Figure 1. OUTs dilution curve of each sample

accounted for 29.7% and the subjects with decreased Enterococcus 43.2%. It is further indicated that probiotics can increase the proportion of beneficial bacteria in the gut microbiota of some diabetics and reduce the proportion of harmful bacteria.

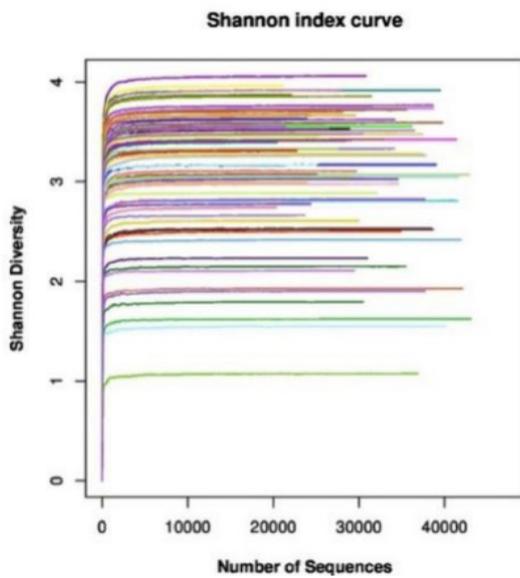


Figure 2. Shannon index curve of each sample

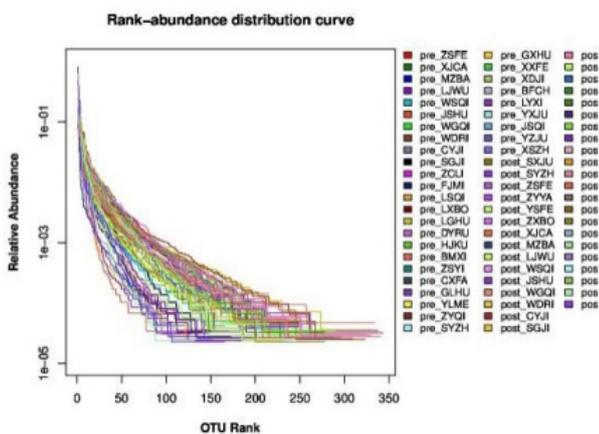
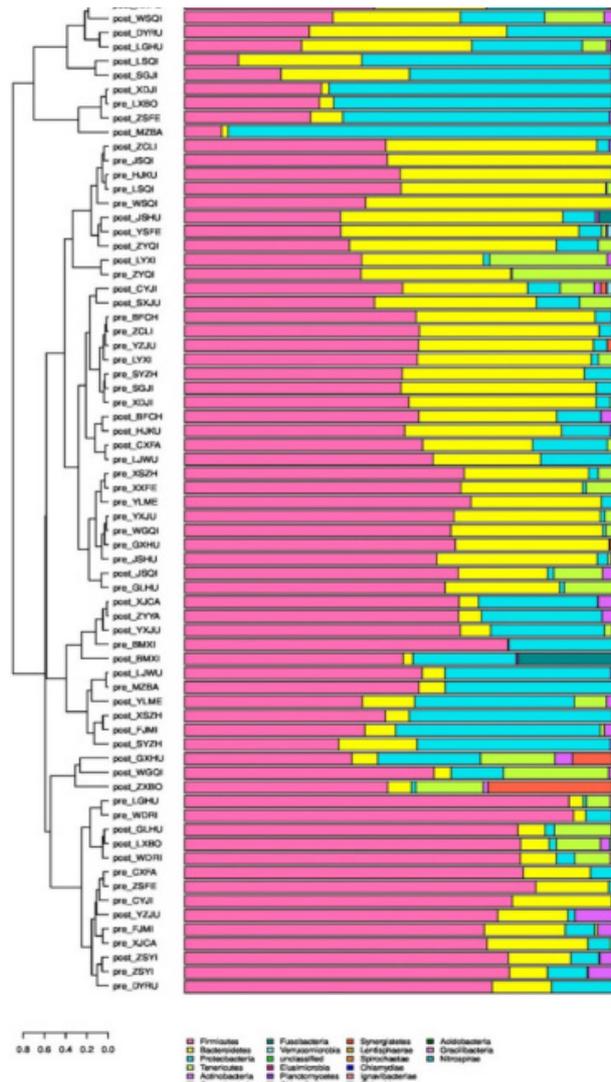


Figure 3. Runk-Abundance curve of each sample



4. Discussions

Commensal intestinal bacteria and their metabolites are involved in metabolic abnormalities and diseases by affecting the host's metabolism and immune system. Studies have found that patients with abnormal glucose metabolism are accompanied by an imbalance of gut microbiota. On the one hand, the number of gram-negative bacteria increases causing the increases of lipopolysaccharide (LPS). After LPS enters the human body and is recognized by immune cells, it produces multiple inflammatory factors and induces the occurrence and development of systemic chronic inflammation [3,4]. On the other hand, the bacteria producing butyrate decreases, increasing insulin sensitivity, and weakening the barrier function to reduce inflammation and protect intestinal mucosal, and then inducing the occurrence and development of diabetes [5]. Metagenome technology refers to the technology to directly extract the total DNA from the environment to study the sum of microbial genes without the microbial culture stage. 16srRNA high-throughput sequencing technology used in this study is the main method of metagenome technology. The variable region of bacteria 16srRNA gene has the species specificity and the taxonomic characteristics of bacteria can be obtained by analyzing the sequence of the variable region. Therefore, this method is more accurate and specific than the traditional PCR method. In this study, Type 2 diabetes patients took orally probiotics for joint intervention for 24 weeks. The intestinal bacteria were classified and identified and accurately quantified by high-throughput sequencing at baseline and after intervention

respectively. The results showed that all samples from all subjects had enough test depth and abundant species, reflecting the microbial information in samples. In this study, the Firmicutes, Bacteroidetes, and Proteobacteria were the dominant bacteria in the intestinal tract of the subjects with Type 2 diabetes. After 24 weeks of intervention, the number of the subjects with significantly increased Firmicutes, Actinobacteria, and Cyanobacteria in the samples increased, indicating that the flora structure of each sample changed after intervention. The study has shown that the proportion of Actinobacteria/Firmicutes and Firmicutes/Bacteroidetes in patients with Type 1 diabetes decreased, and that the beneficial bacteria producing butyrate decreased [6]. The sequencing results of this study were similar to the above. After the intervention, the proportion of Firmicutes, Actinobacteria and Cyanobacteria in some samples increased significantly, and the Lactobacillus under Firmicutes increased. Cluster analysis showed that most samples in the post- group and the pre- group could cluster in the group, indicating that the probiotics in this study changed the proportion of all types of bacteria in the gut microbiota of Type 2 diabetes patients and there were some similarities in the changes of flora.

Comparing the glucose and lipid metabolism indexes of subjects at the baseline and end of the trial, it was found that after the intervention, fasting blood glucose (FBG) was significantly improved, blood lipid standard-reaching rate increased, HOMRIR index decreased, and insulin resistance was improved. At the end of the trial, the number of subjects

with increased intestinal probiotics and with decreased conditional pathogens all increased. The subjects with increased Bifidobacterium under

Actinobacteria in probiotics increased by 62.2%, and the subjects with increased L.Lactobacillus that belongs to Lactobacillus under Firmicutes increased by 21.6%. It is considered that these changes are related to probiotics intervention combined with this research plan. Changle capsule contains Bifidobacterium bifidum, Lactobacillus acidophilus, and Streptococcus thermophilus, without hypoglycemic components. The effect of Jiangtangqi granule is to increase the sense of satiety and reduce the intake of other foods by taking it before meals, so the diet variation of each patient can be well controlled. The carbohydrate in the granule plays a role similar to prebiotics, conducive to the absorption of probiotics in the Changle capsule and reproduction in the intestinal tract, but there is no composition of directly reducing blood glucose in the capsule. In this study, joint intervention by increasing probiotic intake is used to effectively supplement the probiotics/prebiotics and regulate the metabolism of fatty acids to regulate the gut microbiota of Type 2 diabetes patients, thus improving fasting blood glucose at the end of the trial. Animal studies showed that the rats fed a high-fat diet were fed with probiotics in advance, which has certain preventive effects on the formation and development of Type 2 diabetes in the rats. Moreover, the hypoglycemic effect of probiotics is related to the improvement of the structure of gut microbiota, inhibition of the reproduction

of harmful bacteria, reduction of the expression of inflammatory factors TNF- α and IL-6 [7]. Amar, et al. found that Bifidobacterium and Lactobacillus could change the early bacterial translocation in the rats with diabetes induced by a high-fat diet, thereby reducing the expression of some cytokines such as TNF- α , IL-1 β , PAI-1 and IL-6, and improving insulin sensitivity and glucose metabolism [8]. Therefore, now many scholars believe that probiotics, as a kind of active microorganisms regulating the intestinal microecological balance of the host, can improve energy metabolism in the body, reduce chronic inflammation and oxidative stress by changing gut microbiota and its metabolites. The application of probiotics has gradually become a research focus in preventing and controlling the occurrence and development of Type 2 diabetes [9].

In this study, after increasing the probiotics intake, no obvious abnormality found in the liver and kidney functions of patients, and the subjects had no obvious discomfort, so this method has better safety. Although the results showed that the gut microbiota changed after the intervention, and the glucose metabolism, insulin resistance and lipid metabolism were improved, the correlation analysis and attribution analysis could not be well made because of the less strict grouping and more

confounding factors before intervention. Therefore, we should strictly group and increase the sample size in future study. Meanwhile, inflammatory indexes and oxidative stress indexes should be measured and determined for correlation analysis and attribution analysis. In conclusion, the intake of intestinal probiotics can

regulate the gut microbiota of Type 2 diabetes patients, promote fasting blood glucose to reach the standard, and improve insulin resistance to help lipid metabolism reach the standard.

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Thoracic Endovascular Aortic Repair for Type B Aortic Dissection

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ABSTRACT

The incidence of aortic dissection (AD) is estimated to be 1 in 100,000 per year. The onset and progression of AD are rapid. Failure to receive appropriate treatment might lead to death in a short time. Even following active treatment, patients might develop low cardiac output syndrome, severe infection, and hemorrhage, which lead to death. Interventional therapy is a surgical method that has been widely used in Stanford type B AD recently. It is characterized by minimal invasiveness, low incidence of postoperative complications, and low cost. This article will review the interventional treatments for AD and will guide the selection of treatment options.

Keywords: Aortic dissection; Interventional therapy; Indications; Complications

1. Introduction

Aortic dissection (AD) is a fatal vascular disease that occurs when blood leaks through an intimal tear in the aorta, passes into the artery wall and eventually forms a dissected hematoma, where true lumens (TLs) and false lumens (FLs) expand along the long axis of the artery. The occurrence of AD is mainly associated with hypertension, which induces long-term oxidative stress in the arterial wall, resulting in cystic degeneration or necrosis of the elastic fibers, and the formation of dissection. If AD is not diagnosed or treated appropriately, the early (within 1 h) fatality rate of patients with AD could reach 1%. Timely surgical treatment and the administration of medications significantly improved the survival rate of patients with AD, with a decrease in the

case fatality rate from 27% to 18%. Stanford type B AD includes dissections that originate in the descending thoracic aorta, abdominal aorta, and iliac artery, which account for 25%–40% of all AD cases. Approximately 75% of type B AD is noncomplicated AD. Thoracic endovascular repair of the thoracic aorta (TEVAR), which is known as thoracic aortic interventional therapy, is a minimally invasive surgical method that is used for the treatment of critically ill patients with AD and is superior to open surgery in some aspects [5,6]. Due to the advances in medical technology and equipment, TEVAR has been applied gradually for the clinical treatment of Stanford type B AD. This article will review the interventional treatments for Stanford type B AD and will provide guidance on the selection of interventional

therapies.

2. Indications and Contraindications of Interventional Therapy

In interventional therapy, endovascular stents or covered endovascular stents are commonly used to close the tear and FLs, and therefore, restore the patency of the TLs. Aortic intima fenestration and stent implantation are performed to restore blood perfusion in ischemic areas. Interventional therapy is suitable for patients with chronic heart failure, chronic kidney insufficiency, and chronic pulmonary insufficiency, and those who have previously been treated with thoracotomy. The indications for interventional therapy for patients with early-stage AD are: (1) duration of chronic type B AD > 3 weeks and (2) length of the neck hemangioma is > 1.5 cm. Due to the advances in medical equipment and technology recently, the indications for interventional therapy have changed. Patients who are diagnosed with acute type B AD with possible aortic rupture, branch organ ischemia, aortic aneurysm formation, intractable severe pain, or hypertension might qualify for interventional therapy.

The optimal treatment for acute type B AD remains controversial. Some researchers found that the early and medium-term mortality of patients with thoracic aortic disease that were treated with interventional therapy was lower than those who received other treatments, in particular, conservative medical treatment. Therefore, currently, the indications for TEVAR for the treatment of AD are: (1) rupture and bleeding of a dissected aorta; (2) diameter of the dissected aorta increases rapidly (≥ 10

mm/year); (3) ischemia occurs in vital aortic branches; (4) persistent and unrelieved pain; (5) formation of intramural hematomas and aortic ulcer; and (6) formation of an aneurysm with an approximate diameter of 50–60 mm.

Although TEVAR has been widely used to treat AD, it is not recommended for patients with systemic infection, an inappropriate vascular approach, or inadequate anchoring area.

3. The Main Surgical Approaches in Interventional Therapy

TEVAR procedures mainly include aortic covered stent implantation, aortic fenestration, chimney technology, and branch stent technology. Aortic covered stent implantation was first performed in Argentina in 1990 to treat abdominal aortic aneurysms. Percutaneous transluminal aortic stent implantation was first used in 1994 to treat thoracic aortic aneurysm and descending AD. In this surgery, a covered stent is placed in the TLs to block the rupture of the dissection, reduce the blood flow through the FLs, induce thrombosis, and decrease the pressure in the FLs, and therefore, decrease the risk of aortic dilatation and rupture. In addition, the expansion of the TLs improves branch vascular perfusion and stabilizes the dissection. The aortic stent implantation shortens the operation time and reduces trauma, and significantly decreases the incidence of complications and mortality in patients with AD. Zhou et al. investigated the effect of stent-graft implantation for the treatment of patients with acute or subacute Stanford type B AD. The clinical data for 38 patients (31 males, 7 females) who presented with Stanford type

B AD and received TEVAR treatment were retrospectively analyzed, which included 22 cases in the acute stage and 16 cases in the subacute stage. The average diameter of the TLs and FLs within the dissection before and after TEVAR, and the maximum aortic diameter, were measured. Seven patients (18.4%) had endoleaks following treatment. There were no perioperative deaths in this cohort. The results of computed tomography angiography at baseline showed that there was no significant difference in the maximum aortic diameter, or the diameter of TLs or FLs before TEVAR between the acute and subacute groups ($p = 0.193$, $p = 0.301$, and $p = 0.067$, respectively). After TEVAR treatment, significant differences were observed in the maximum aortic diameter and the diameter of FLs between both groups ($p = 0.005$ and $p = 0.012$, respectively), but not in the diameter of TLs ($p = 0.069$). The diameter of the TLs increased, and that of the FLs in the acute and subacute groups decreased significantly following TEVAR ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p = 0.007$, respectively). The maximum aortic diameter in the acute group significantly decreased ($p < 0.001$), but no significant changes were observed in the subacute group ($p = 0.121$). These findings suggested that the short-term prognosis for patients who received TEVAR in the acute stage was similar to that of the subacute group, although better outcomes were observed in patients with acute AD.

In aortic fenestration, the fenestration position and fenestration diameter of the branch arteries are determined by imaging examination. Holes and fenestrations are made on the inner membrane to separate TLs and

FLs, decompressing the hypertensive FLs, and therefore, restoring blood supply. Aortic fenestration is used to increase the length of the stent; therefore, the anchoring area of the stent has a better fit on the aortic wall, which makes it suitable for AD patients with complications, such as visceral or lower limb ischemia. In addition, fenestration is performed in patients with ischemic manifestations, such as gastrointestinal ischemia, acute renal failure, claudication, or pulseless limbs. Fenestration relieves ischemic symptoms in approximately 85%–93% of patients, stabilizes AD, and increase the time for elective surgery or stent intervention, and therefore, improves the prognosis of patients with AD. Kuo et al. evaluated the efficacy and safety of a handmade fenestrated stent-graft over an aortic stent graft to preserve the left subclavian artery (LSA) in TEVAR. A total of 32 patients with various thoracic aortic pathologies were included. There were 24 patients (75.00%) with AD, 5 patients (15.63%) with thoracic aortic aneurysm, and 2 patients (6.25%) with penetrating aortic ulcer. One patient (3.13%) required re-TEVAR due to the endoleak and sac expansion from previous TEVAR for a thoracoabdominal aneurysm. They were treated with TEVAR, in which handmade fenestration over a thoracic aortic stent-graft was used for the LSA. TEVAR on zone 2 landings with single fenestration for the LSA was performed in 26 patients (81.25%); TEVAR on zone 1 landing with double fenestration for LSA and left common carotid artery was performed in 5 patients (15.63%); TEVAR on zone 1 landing with single fenestration for the LSA and a chimney graft for the left common

carotid artery was performed in 1 patient (3.13%). The technical success rate, defined as the successful alignment of fenestration to the LSA, was 93.75%. At a mean follow-up of 17.3 months, four cases of endoleak and two cases of stent graft-induced new entry were observed; three of them were treated endovascularly. The ability to preserve blood flow in the LSA using a handmade stent-graft fenestration might justify the use of TEVAR in emergency cases. In addition, fenestration surgery can be used as adjuvant therapy in emergency treatment or stent implantation to reduce the incidence of ischemic complications. Recently, fenestration and branch endovascular stent implantation have shown promising clinical results for the treatment of branch vascular ischemia.

During transluminal therapy that uses the chimney technique, the vital branch vessels, such as the LSA, are intentionally or inadvertently covered due to the inadequate anchoring area. Bare stents and covered stents are often anchored together to preserve the branch vessels. This technique was first proposed by R. K. Greenberg and then applied to TEVAR. The chimney technique is not performed as a routine surgical approach for complex Stanford type B AD, it is used in patients who cannot tolerate hybrid surgery or open surgery, or in an emergency. Since this technique preserves vital branch vessels and maintains the blood supply to vital organs, it might replace bypass or open vascular repair in the near future. Zhao et al. analyzed the effects of different chimney techniques that were applied to different positions on the aortic arch and provided guidance to reduce the complications from

chimney thoracic endovascular aortic repair (cTEVAR). In this study, 234 patients with AD that involved the arch branches were treated with cTEVAR. There were 156 cases (66.7%) with single chimney (SC), 48 (20.5%) with double chimney (DC), and 30 (12.8%) with triple chimney (TC). A total of 342 chimney grafts were used. The results showed that all chimney grafts were successfully implanted, and no migration or occlusion was observed during follow-up. The postoperative mortality rate was 1.7% (4/234) and the occurrence of cerebrovascular events was 1.3% (3/234). In addition, 75 cases (75/234, 32.1%) had type I intimal leakage during the operation. The leakage in 27 patients (27/75, 36.0%) disappeared during follow-up; 33 patients (33/75, 44.0%) had stable FLs; 15 (15/75, 20%) had FLs expansion and were successfully treated with endovascular embolization. Patients with a proximal tear that was located in zone 0 had a higher instant endoleak rate than those with the tear located in zones 1, 2, and 3 ($p = 0.041$, $p = 0.042$, and $p = 0.009$, respectively). Patients with TC had increased instant endoleak than those with SC ($p < 0.001$) and DC ($p = 0.012$). However, during follow-up, there was no significant difference in instant endoleak between the groups. These data showed that the SC technique achieved satisfactory results.

A retrospective study on 234 patients with aortic arch disease was performed to evaluate the feasibility, effectiveness, and safety of chimney, fenestration, and in situ fenestration techniques. Among them, 126 patients received cTEVAR (98 cases with SC, 24 cases with DC, and 4 cases with TC); 102 patients (102/234)

were treated with surgical fenestration (92 cases with single fenestration, 9 cases with double fenestration, and 1 case with double fenestration and innominate arterial chimney); the remaining 6 received in situ acupuncture fenestration. The indications included AD (99/234), aortic arch aneurysm(60/234), penetrating aortic ulcer (72/234), and re-intervention (3/234). There were five early all-cause deaths. The technical success rate was 99.6% and the patency rate of all branches was 99.6%. There were 15 cases with type Ia intestinal leakage; 14 cases (11.1%) in the chimney group and 1 case (1%) in the table fenestration group. Five patients underwent re-intervention. The median follow-up for all patients was 28 months (range: 16–41 months), which indicated that chimney, table fenestration, and needle fenestration techniques were feasible, effective, and safe methods for the treatment of aortic arch lesions.

The Castor branched aortic stent, which was produced in China in June 2017, is a new type of thoracic aortic stent that has been used globally. This stent has a unique integrated structure, which better fits with the blood vessels of Chinese patients and shows improved stability and a low risk of long-term displacement. It allows precise positioning, separates TLs and the FLs, and avoids the use of hybrid technique and staged operation to reduce the pain of patients. The origin of the LSA can be intentionally covered by a stent-graft to provide an adequate proximal landing area during the endovascular repair of the Stanford B AD. Jing et al. retrospectively analyzed 73 patients with Stanford type B AD who were treated with the Castor stent-graft in 11 tertiary

hospitals in China. There were 50 cases with acute AD (<2 weeks [68.5%]) and 23 cases with chronic AD (>2 weeks [31.5%]). The results showed that the surgical success rate was 97% (n = 71/73). Two of the failures were caused by partial occlusion of the branches of the stent-graft. Four patients had intraoperative endoleaks (type Ia: n = 2, type B from the LSA: n = 2) and the endoleak rate was 5% (n = 4/73). One patient died in the hospital and the rest had no major complications. The mortality rate within 1 year of post-operative follow-up was 5% (n = 4/73) and the mortality rate within 6 years was 7% (n = 5/73). The cause of death in two patients was unknown. The deaths of three patients were not related to the aorta. Two patients had a new breach at the proximal or distal edge of the stent-graft and underwent endovascular repair. The branches where the Castor stent was deployed were partially occluded in 6 patients, and the follow-up patency rate of the branches was 93% (n = 63/68). In two cases with intraoperative endoleaks that were not treated, the endoleaks disappeared during follow-up. These findings suggest that endovascular treatment that used the Castor single-vessel stent graft was an easy-to-operate, safe, and effective treatment option for TBAD patients whose stents needed to be anchored near the origin of the LSA. The intraoperative reconstruction of the LSA resulted in a better blood supply and fewer complications.

4. Complications of Interventional Therapy

The complications from interventional therapy include internal leakage, distal new

rupture, stent displacement, vascular injury, and thrombus exfoliation. Internal leak- age, which is the most common complication, occurs when the covered stent implantation in the aorta does not completely isolate the aneurysm cavity from the arterial blood flow. The incidence of internal leakage with stent treatment of AD was 3%–44%, which was related to the physical condition of the patient, type of the stent, anatomical condition of the aortic aneurysm, and the experience of the operator. Approximately 50% of the internal leakage disappeared spontaneously. However, it might expand to form an aneurysm and could lead to the rupture of the aneurysm cavity. In this case, re-implantation of the stent is required.

Stent displacement is a common complication in interventional therapy that mainly occurs due to intra-aortic blood flow and pulsation after stent implantation. Stent displacement increases the risk of internal leakage and might cause serious consequences, such as aortic rupture. Therefore, during the operation, it is important to ensure that there is no dilation or lesion at the anchorage site of the aorta and stent. To prevent stent displacement it is important to select an appropriate stent, the diameter of the proximal and distal stent should be 3 mm ~ 4 mm larger than the diameter of the hemangiomas, to avoid stent distortion and angulation.

The incidence of new distal rupture is 3.4%–27.8% and the mortality rate is 26.1%. When the length of the stent is >145 mm, the incidence of fracture significantly decreases. The oversizing area is closely related to the risk of stent-derived rupture. The stress

between the stent and the aortic wall is the main factor that affects the distal aorta. To prevent distal rupture, lengthening the stent has been suggested, reducing the oversizing area, and the stress between the stent and the aortic wall, and protecting the edematous vascular wall in the acute stage.

5.Summary

The clinical significance of interventional therapy for the treatment of AD has been increasingly recognized.

Stent therapy could replace traditional surgical treatment in most cases. In addition, it could be performed in patients who cannot tolerate surgery. Due to the development of technologies and materials, the suture-free elephant trunk stent with artificial vessels and branch vessels has been used in type B AD with ascending and arch expansion. New stent materials, such as Ni-Ti alloy extruded stent and Ni-Ti memory alloy have been gradually used in clinical practice. New interventional guidance, such as visual guidance, virtual reality imaging technology, magnetic navigation guidance, and esophageal ultrasound guidance, shows the internal structure of the cardiovascular system and provides real-time monitoring for physicians during an operation. In addition, blood transfusion is not required in interventional therapy, which decreases the operation time and reduces operative morbidities and costs. The use of new dynamic imaging technology might facilitate the exploration of the morphology and dynamics of the aorta; therefore, new stents could be designed for patients with AD for a better prognosis.

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Disclosure of Interest

The authors report no conflicts of interest.

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Discussion on the Challenges Surrounding Anti-microbial Resistance, Using Relevant Case-study Examples

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ABSTRACT

The advent of antimicrobial drugs has made a huge contribution to human society, but their commodity nature has given rise to behaviors such as abuse and overuse, leading to the emergence of resistance to antimicrobial drugs and other hazards. Nowadays, the structure of interests formed by various stakeholders in the market circulation of antimicrobial agents has become unbalanced, and government intervention as a breakthrough still faces many challenges. This paper discusses the AMR challenges of government intervention under the interest structure in the context of case studies in the Global North and the Global South areas from the point of view of human health in terms of stagnant R & D processes for novel antimicrobial drugs, a profit-oriented neoliberal atmosphere that mismatches production trends of antimicrobial drugs with market demand, the prevalence of private institutions lacking effective regulation, incomplete government interventions, and the difficulty of pursuing the WHO strategic plan on antimicrobial resistance, etc.

Keywords: Anti-microbial resistance; State intervention; Interest structure; Case studies in the Global North and the Global; South areas

1. Introduction

Since the advent of antimicrobial drugs, they have not only made great contributions to human society but also brought serious hazards such as drug resistance which was defined by WHO as a phenomenon that ‘bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines’. With the spread of drug resistance over all the world, a post-antibiotic era in which there are no medicines available will emerge as it has become increasingly difficult and costly to treat infections and antimicrobials tend to be less

effective. According to a 2016 estimate by a UK economist O’Neill, the number of deaths caused by drug resistance will exceed 10 million by 2050 if effective actions are not taken. Meanwhile, the World Bank and the Food and Agriculture Organisation of the United Nations (FAO) forecast in their research that in 2050, there would be a 1.1% to 3.8% decrease in the annual global GDP. The WHO has declared antimicrobial resistance to be one of the top ten global public health threats to humanity with the misuse and overuse of anti-microbial drugs being one of the primary drivers.

Ultimately, antimicrobials circulate in the market as a unique commodity. According to the nature of the product, the use of antimicrobial drugs is divided into six stages, including development, manufacturing, purchase, operation, provision, and consumption. In this process, an interest structure is formed through the checks and balances between the various stakeholders at each link. However, the imbalance of interests and the absence of outside intervention in advance lead to market failure, antimicrobial proliferation, and uncontrolled drug resistance (Figure 1). Necessarily, a breakthrough is supposed to be government intervention.

As a result, this article aims to discuss the challenges of AMR in state intervention under

the interest structure only from the point of view of human health (other areas of use including food-production, agricultural, aquaculture and so on). The first section describes the current issues of state involvement in the changing dynamics of interest relations at national and international levels through the six aspects mentioned above, and contrasts them by referring to case studies in the Global North and the Global South areas. The second section summarises the limitations of the paper including the problems of government interference itself. Last but not least, based on the challenges identified, several recommendations are made to tackle AMR in the context of national interventions.

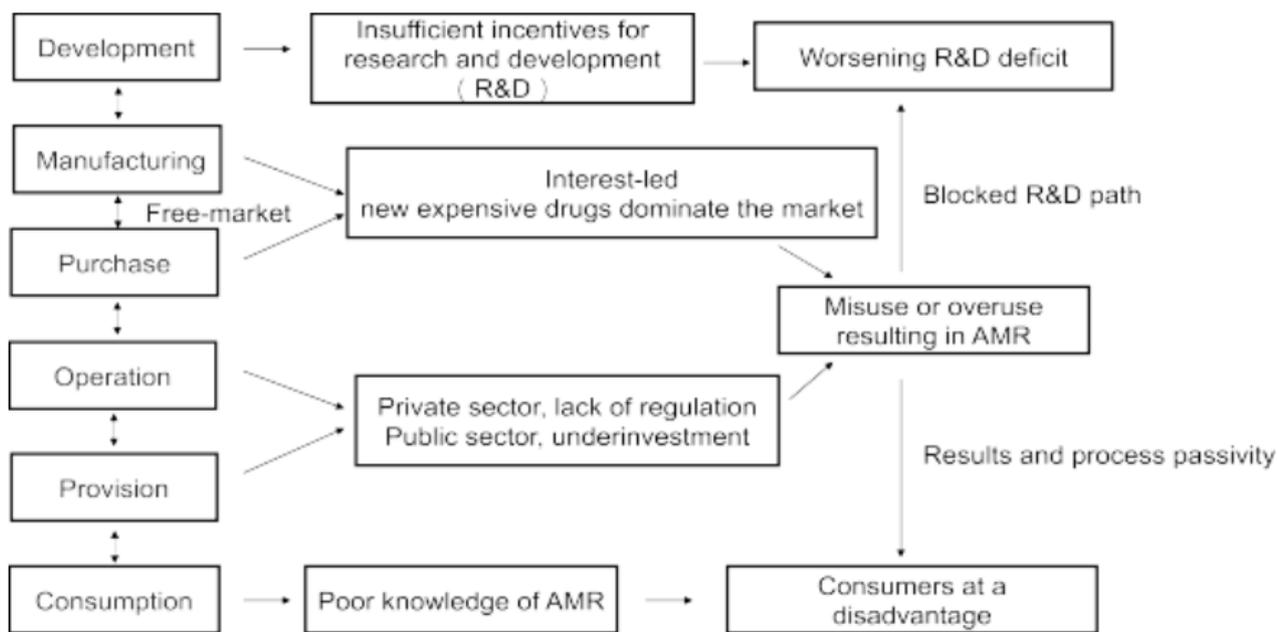


Figure 1. The Relationship Between Imbalance of Inter-ests and AMR.

2.Challenges

2.1Development Stage

At the international level, there is no explicit division of labour in each country. The rapid growth of anti-microbial resistance levels in countries including Brazil, Russia, India, China, and South Africa (BRICS) accounted for three-quarters of a 36% increase in the consumption of antimicrobials in 71 countries from 2000 to 2010. Although a report has shown that the British government recently confirmed a financial examination of economic issues pertaining to antimicrobial resistance and a strategy to promote and facilitate the development and production of new generations of antimicrobials, the situation remains critical. In the 1990s, almost 20 companies were active in antimicrobial development around the world. At present, only GlaxoSmithKline and AstraZeneca are still among the world's pharmaceutical firms with antimicrobial testing programs. In order to alleviate the global crisis of AMR and the shortage of antimicrobial drugs, the key point of the 2014 Commission chaired by the former Goldman Sachs economist Jim O'Neill was to stimulate antimicrobial researches and innovations with active incentives. Nevertheless, hurdles or obstacles remain. Firstly, in terms of incentives, pharmaceutical companies are gradually abandoning antimicrobial research teams in favour of fields that may not be 'easier' to explore but certainly have better economic returns as the process of discovery is time-consuming and expensive. For example, compared with less than 50 antimicrobial products, almost 800 new drugs were produced

in 2014 in the field of oncology. Secondly, the financial assistance offered may be overdue or the determination of the appropriate amount of bonus could be difficult and eventually, all risks are borne by governments or other investors.

As for the current regional policies such as the Generating Antibiotics Incentives Now (GAIN) Act in the USA, and the Innovative Medicines Initiative (IMI) in Europe, the economic stimulus packages are inadequate and burdensome, even though initiatives have been suggested to boost the production channels for new antimicrobials. For instance, the GAIN Act does not address antimicrobial stewardship measures. Without the effective management of new antimicrobials, they are mostly used as a last resort therapy, which is impossible to obtain benefits for market exclusivity. In the absence of sufficient usage of new antimicrobials, consequently, the effective life of new antimicrobials was shortened, and the reward impact of the GAIN Act was decreased due to the resistance condition aggravated by the abuse of antimicrobials. Only if push and pull strategies operate together in the drug development environment will the best incentives be accomplished.

2.2Manufacturing and Purchase Stages

With regard to AMR, different political parties have their respective positions. Three types of welfare states are recognized, including liberalism, social democracy, and nationalism, among which neoliberalism is characterized by the highest level of commodified services that are extremely distinctive and wide in scope and advocates less interference from the state. Therefore, interfering in strategies to minimize

AMR in a neoliberal environment faces many challenges.

Although the role of the free market is emphasised in the neoliberal theory, the absence of external intervention is likely to cause severe consequences in the case of antimicrobial resistance as with the initial commercialisation of penicillin and many other antimicrobial compounds. In the 1940s, a vast number of pharmaceutical companies participated in the development of antimicrobials and the price of unpatented medications such as penicillin plummeted as funding grew. With the great demand for penicillin daily products, such as toothpaste, makeup, and other forms of consumer necessities, pharmaceutical firms have expanded the market under the guise that penicillin could not only cure bacterial infections but also benefit healthy people by preserving the efficacy of removing daily germs. After successfully inventing and patenting new antimicrobials, they increased their investment in the pharmaceutical industry and raised the price of these anti- microbials, as well as their manufacturing volumes regardless of the need. As a consequence, in the 1960s, many needless medications emerged in the market, resulting in a pattern that lasted until antimicrobial research programmes dried up in the 1980s when the pharmaceutical industry turned its focus to other more lucrative drugs.

Neoliberalism probably provides the overarching philosophy for the analysis of these economic developments in relation to AMR, affecting the restricted or counter-productive role of governments in facilitating actions that effectively regulate AMR.

Furthermore, the relationship between the industry out- put and the market demand is not completely exploited in neoliberalism to tailor production according to changes in the market demand. One successful case is the ban on the use of antimicrobials on cattle by Namibia after its European consumers refuse to eat food-borne meat antimicrobials. It is a rare example of Namibia's prompt modification of its approach to market demand so as to sustain its sales market and reduce its AMR.

2.3 Operation and Provision Stages

Based on their ownership, major stakeholders in operation and provision stages can be divided into two categories, namely the public and private health sectors. What needs to be made clear is that private clinics and doctors act as operators and providers in the private system, while in the public system, the government acts as an operator and the public health sector as a provider.

The last two decades have witnessed the tremendous expansion of the private health care sector, especially in South Asia where 80% of patients were expected to receive treatment in private hospitals and in India where 93% of health facilities were provided in private sectors. Despite services provided by private sectors for individuals whose needs cannot be met by public organisations, there is a lack of effective regulation in private sectors when compared with the public health sector, especially in Low- and Middle- Income Countries (LMICs), which constitutes a severe threat of AMR . Firstly, differences in the quality of clinics have widened gaps in access to health services . In most South Asian

countries such as Pakistan and Bangladesh, few structures or tools are available for tracking and controlling private sectors, leading to the fact that active institutions are operated by untrained providers. Secondly, it is a normal phenomenon that untrained or inexperienced individuals run pharmacies because of the limited control over the qualification for the sale of specific types of drugs, which directly leads to misdiagnosis, confusion, or inadequacy. Thirdly, commercial companies prefer to store a vaster array of antimicrobials than municipal hospitals without the desire to indiscriminately administer or prescribe them. In addition, the sale of antimicrobials on the internet as a form of online privatisation is the same case. One survey showed that without prescriptions of antimicrobials, a third of the 138 separate vendors listed as antimicrobials suppliers were selling them. Fourthly, doctors with the lowest credentials were found to have the lowest fees in general. However, they saw the largest number of vulnerable patients at the risk of infectious diseases, including Tuberculosis (TB), HIV, and Malaria. Fifthly, the poor quality of medicines and the profit margins between various clinics intensify the pressure for options, leading to a flood of substandard and spurious medicines into the market. According to the statistics, the annual sales of falsified and adulterated pharmaceuticals in Peru and Columbia were about \$66 million and \$60 million, respectively. In accordance with the above five points, it can be concluded that private organisations lacking monitoring and management systems are more likely to have issues in the diagnostic process that may form an anti-microbial resistance

vicious circle (Figure 2).

The public health care sector faces multiple challenges caused by the local political structure, economic status, and social patterns. First and foremost, universal health promotion strategies, namely Infection Prevention and Control Interventions (IPCIs) proposed by WHO, have gained success in some domains in LMICs. For example, washing hands with soap in Karachi, Pakistan has not only halved diarrhea and acute respiratory infections but also decreased the occurrence of pustules that would require antimicrobials by 30%. However, the implementation of such strategies remains difficult as there is a frequent lack of access to even simple mechanisms, as well as a poor empirical base to justify their incorporation into such healthcare contexts. Furthermore, government investment in infrastructure is far from being adequate. In spite of the importance of water and water-related devices for alleviating the transmission of AMR bacteria, basic clean water, sanitation, and hygiene facilities are not well-established in parts of developing countries to cut off AMR's environmental transmission pathways [18,19]. For example, open defecation is still occurring in many heavily populated areas such as India. More industrialised countries such as the United States and the UK are facing ageing facilities and the demand for more sophisticated and sustainable water treatment technologies.

2.4 Consumption Stage

In order to reduce AMR, WHO presented an international action plan in 2015, one of the strategic objectives of which is 'to improve awareness and understanding of antimicrobial

resistance’, and steps have been taken by several nations, such as the European Antibiotic Awareness Day campaigns. However, surveys (Table 1) of the public’s knowledge and perceptions about AMR from four typical countries (Sweden, USA, Japan, Nigeria) revealed that there were still many obstacles in the consumption process of antimicrobials in both the Global North and the Global South areas. Despite the limitations of the surveys due to the sample size and respondent bias, they still have a reference value.

At first, consumers had poor knowledge of the appropriate use of general antibiotics.

They did not know when antibiotics should be used. In Japan, for example, only 22% of respondents recognised that antibacterial medications could not kill viruses and 45.5% of them obtained antibiotics due to the cold. In the United States, almost 40% of respondents felt that antibiotics were the best way to treat cold symptoms and the proportion was 13.4% in Sweden where AMR was low.

They did not know how to choose the right antibiotics. According to the Nigerian report, people tended to purchase and use the

same antibiotics that had cured their previous diseases.

They did not know how to use antibiotics correctly. For example, about 26.1% of Nigerian participants avoided taking antibiotics when they felt better instead of taking all them as instructed. Also, 23.6% of Japanese participants reported the halt or adjustment of their antibiotic doses on their own.

Next, storing antibiotics were more common in developed countries with a 31% storage rate in Nigeria compared to 12% in Japan. Preserving antibiotics could be a temptation of self-use (e.g., self-treatment, avoidance of flu) but improper storage and expired antibiotics may lead to allergic reactions and increase the possibility of sharing them with others.

Besides, the persistent absence of information by patients will produce an unfair interaction with doctors. As mentioned above, people could rely on professors who might be more susceptible to external factors such as pharmaceutical firms to prescribe profit-related or counterfeit drugs.

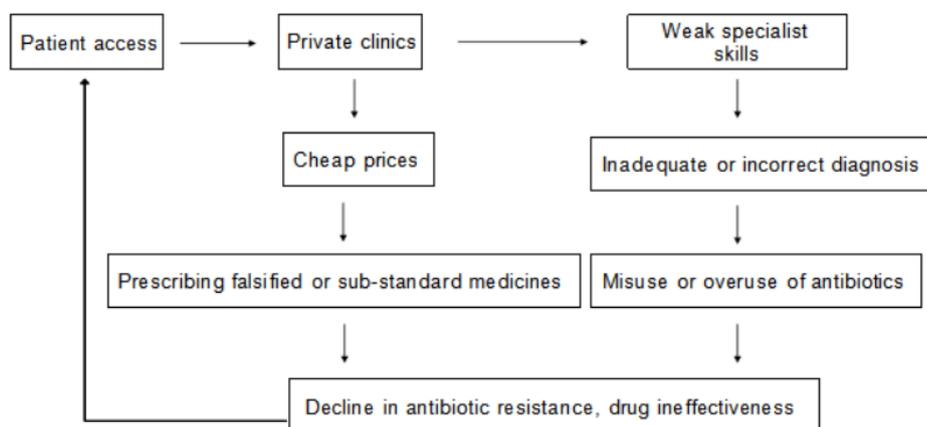


Figure 2. An Anti-microbial Resistance Vicious Circle

Table 1. Surveys from Four Countries of Public's Perceptions and Knowledge about AMR

Country	Swedish	America	Japan	Nigeria
Characteristics	Global North low AMR	Global North	Global North	Global South
Subjects of Survey	public	public	public	public
Number of participants	1426	215	3390	482
Agree that antibiotics cannot effectively fight against viruses (%) (right statement)	77%	70%	22%	
Agree that antibiotics can effectively fight against cold and flu (%) (wrong statement)	13%	less than 25%	three-quarter (75.4%)	44%
Store antibiotics (%)			12%	31%
Level of knowledge of the relevant terms	29.50% of interviewees are with accurate knowledge.		4 out of 10 interviewees had heard the term 'AMR'	8.3% of interviewees are with accurate knowledge; 7.3% of interviewees had heard the term 'AMR'; 56.45% of interviewees had heard the term 'antibiotic resistance'; 46.9% of interviewees had heard the term 'drug resistance'; 17% of interviewees had heard the term 'AMR'.
Use over the counter (OTC) antibiotic drugs (%)			3%	2%
The most common source of information about AMR		Television and the Internet	TV news or newspapers (25.7%) doctors (19.1%).	doctors/nurses (50%) pharmacists (31.3%) specific campaigns (8.5%) media (9.8%)

3. Conclusions

This article has discussed the challenges of AMR in state intervention under interest structure from six perspectives (developing, manufacturing, purchasing, operating, providing, consuming) based on the use of antimicrobial drugs.

Owing to a lack of consistency in the government's external division of labor and inadequate domestic economic recovery measures, the research and development process of new antimicrobials has stagnated.

A free market between production and purchase was established in a neoliberal atmosphere, and the principle of benefit was encouraged above all else. However, the AMR proved to be worse and worse without government interference, making clever use of the relationship between production trends and market demand.

In recent years, private clinics have become more prevalent as a cornerstone of the operating phase, but the lack of effective government regulatory policies and institutions, particularly in countries with low and medium incomes, has led to a vicious circle of untrained or inexperienced providers mixing and creating AMR.

The government, as an operator, uses interventions such as policy implementation and the distribution by the public health sector of basic services such as vaccines and sanitation to minimize the spread of infectious diseases in public systems, but this remains difficult to do in the near term due to discrepancies between countries.

Countries have used social marketing ads to fulfill the WHO 2015 strategic plan to 'improve awareness and understanding of antimicrobial resistance', but a review of surveys from four typical countries reveals that there is still a long way to go to meet customers with AMR expertise.

In order to achieve checks and balances in the interests of society as a whole, the government, as the most powerful mediator in the whole process, should limit the intentions of abusive subjects by fostering anti-abuse subjects and provide awareness and intelligence to support the acts of anti-abuse subjects by partially or completely opening up information channels.

It should be noted that this paper has been primarily concerned with the point of view of human health; what is needed in the future directions are cross-national studies involving strategic policy analysis of plants and animals to provide more possibilities for addressing antimicrobial resistance.

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A Research on the Relationship between Intestinal Flora and Human Longevity

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ABSTRACT

The exploration of human life and health is advancing with the changes of the times. With the growth of age, the occurrence of chronic diseases of human immunity and organ system is frequent, which has a serious impact on human health. Genes, environment and other random factors determine the outcome of longevity, and intestinal flora is considered to be a decisive factor affecting human health and longevity, mainly because of its huge impact on human immunity, growth and development. The study of the relationship between intestinal flora and longevity is beneficial to improve the health status of the elderly and improve the overall life level of human beings, which has great scientific research value. This review will review the role of intestinal flora in longevity.

Keywords: Intestinal flora; A long life; Life and health

1.The Necessity of Intestinal Microbiota Studies in Longevity Studies

1.1The Intestinal Flora of Normal People

Abundant microorganisms grow in the intestinal tract of the organism, especially bacteria, whose number varies from 500 to 1000 and reaches 10^{12} to 10^{14} . Among them, the number of genes existing in human body is only one hundredth of the number of genes owned by microorganisms, and the number is more than 9.87 million according to relevant data. Intestinal flora is interdependent and interacts with each other to maintain the ecological balance in the intestinal

tract. It plays an important role in intestinal immunity, digestion and absorption, growth and development, and biological antagonism, etc., and constitutes an essential part of life. Intestinal flora can be roughly divided into three categories: 1) Dominant flora: mainly obligate anaerobic bacteria, including Bacteroides, bifidobacterium, Eubacter, lactobacillus, etc., which can be colonized in the deep surface of intestinal mucosa and are beneficial to the health of the host, with low immunogenicity; 2) Opportunistic pathogens: most of them are facultative anaerobic bacteria, including enterococcus and enterobacter, which are not the dominant flora of the intestinal tract. They

are symbiotic with the host and generally not infectious. When the human immune system is low or the intestinal flora is disturbed, it will cause harm to human health. 3) Pathogenic bacteria: they can swim on the surface of the intestinal lumen, and are less likely to colonize in the intestinal lumen for a long time. Most of them are passing bacteria, which will cause damage to human body only when the number reaches a certain level.

1.2 Intestinal Flora and Longevity

Longevity refers to people have a healthy constitution, to ensure the quality of life, and to get a longer life. Factors affecting human longevity are numerous and complex. In general, in addition to natural disasters, human-made disasters, disease, plague and other factors, there are genetic genes, nature, social, family, gender, disease, diet, lifestyle, psychological state and other factors. Back in 1908, a scientist from Russia won the Nobel of “probiotics in the gut” and systematically expounded the association between “beneficial bacteria” and the secret of longevity. They found that the human gut contains 10¹³-10¹⁴ microorganisms, which are mainly bacteria, and their total number is about 10 times that of human cells. The human gut flora is a complex system, mainly in Firmicutes, Bacteroides, proteobacteria, Actinobacteria and Wartinobacteria. However, with the development of science and technology, people gradually realize that the relationship between intestinal flora and human body is not only simple parasitic and parasitism, but also its complex relationship needs to be constantly explored. The intestinal flora indirectly affects human health by affecting the immune system,

causing related diseases, and affecting growth and metabolism, thus acting as a factor affecting human longevity.

2. The Effect of Intestinal Flora on Longevity

2.1 Intestinal Flora and the Immune System

Intestinal flora contributes to antigen exposure in early life and is one of the richest sources of early immune stimulation and adaptation. The continuation of life and health is closely related to the normal functioning of the body’s immune system. The diversity and sufficiency of intestinal flora in normal individuals play an indispensable role in the normal activation of the immune system, so as to ensure the normal progress of the body’s life activities. Innate lymphoid cells (ILCs) and T lymphocytes are widely distributed in the gastrointestinal mucosa, which play an important role in the regulation of intestinal flora and the function of the immune system. At the same time, intestinal flora can also directly or indirectly regulate the growth and development of ILCs. Nikolaeva by normal human and animal physiology such as gastrointestinal tract flora of live microorganisms extracted by drug made of probiotics applied in 60 days weaned 60 newborn calf and 45 days weaned 60 found on big white piglets injected extracted by gastrointestinal flora probiotics drug research object innate immune factors have along with the age and the characteristics of the activated. Intestinal flora plays an important role in T lymphocyte polarization and function regulation. Studies have shown that TLR can be expressed in gastrointestinal epithelial cells to regulate

intestinal flora, activate TLR2- 4 and NF- κ B signaling pathways, secrete regulatory T cell polarizing cytokines, and specifically bind to B cell κ - light chain, thereby ensuring bacterial tolerance and maintaining normal immune function [16,17]. Intestinal flora is an important factor in the immune system of the body, which plays a crucial role in the homeostasis of the internal environment, life health and longevity.

2.2 Intestinal Flora and Chronic Diseases

The harm of chronic diseases is a major obstacle to ensuring the longevity and health of individuals. Intestinal flora is interdependent with the body and plays an indispensable role in maintaining the homeostasis of the body's internal environment and resisting the invasion of foreign pathogens. Abstract: Intestinal flora plays an important role in the regulation of obesity in typical chronic diseases by promoting the production of short-chain fatty acids, reducing the content of fast- induced Adipose Factor (FIAF), and resisting chronic mild inflammatory response. To improve obesity and inflammation. However, long-term high-fat diet can still inhibit the improvement of intestinal microflora structure. At the same time, the increase of gastrointestinal flora promotes the generation of short-chain fatty acid bacteria and plays a certain role in the hypoglycemic effect in the treatment of diabetes. Studies have shown differences in gastrointestinal flora such as Bacteroides and actinomycetes between diabetic patients and healthy subjects, and complex changes were observed during the treatment of low-fat diet through the 6-month follow-up of subjects. Butyrate producing bacteria *Anarunrotruncus* showed a slight increase, while

Roseburia significantly increased at T1 stage, but at later stage gradually decrease. Changes in the structure of gastrointestinal flora and other physical and chemical properties can lead to the destruction of pancreatic β cells and increase the incidence of diabetes. Therefore, the normal diversity and abundance of intestinal flora are important factors affecting the occurrence and development of chronic diseases, and thus play an important role in individual health and longevity.

2.3 Intestinal Flora and Growth Metabolism

Intestinal flora is a complex microbial community in human body, which plays a very important role in cell growth and development, nutrient uptake and other aspects. Gill's team used large-scale shotgun sequencing and 16S RRNa based full-length gene technology to comprehensively understand functional genes of intestinal flora and found that they play a significant role in human metabolic pathways and processes. In addition, there is also A research by used at the same time based on nuclear magnetic resonance (NMR) and mass spectrometry (GC - MS) metabolomics technology, dynamic detection and monitoring of family member's overall metabolic spectrum (urine metabolism of 1 HNMR spectrum) characteristics change, first discovered the human microbiome can affect human body metabolic phenotype, and found that affect the function of human body metabolic phenotype bacteria such as *B.thetaiotaomicron*, *Pseudobutyrvibrio* main sequence Similar to *Clostridium* and *Bacteroidetes*, and related human metabolites were found. In addition, the study of Thaiss CA et al. on intestinal

G- showed that the activation of il-23-IL-22 pathway in myeloid cells inhibited the transcriptional activity of rhythm gene Nr1d1, thus activating NFIL3 and further regulating CD36 and other molecules to promote lipid metabolism in vivo. At the same time, Watad A et al., through their studies on the occurrence and development of diseases in different seasons, showed that intestinal flora can monitor the normal expression of rhythmic lipid metabolic procedures in the body by regulating the transcription of NFIL3 gene in intestinal epithelial cells and some internal clocks, thus further affecting metabolism in the body.

3.Summary and Outlook

With the rapid development of sequencing and genome technology in the scientific field, it has become possible to explore the composition and function of intestinal microbes, and the study on intestinal flora and longevity has also become hot. At present, some existing research from basic research “intestinal flora and regulating mechanism of aging” “gut bacteria to improve the mechanism of different diseases” and “bacteria biological rhythm biohythm of relations” with the host and so on, at the same time, also have to centenarians intestinal flora and its way of life, environmental factors such as the relevance of research. However, intestinal flora is in a complex relationship with the human body to achieve ecological balance in vivo, and can interact with the host through metabolism and genetic inheritance. Therefore, it is very important to reveal the dynamic relationship between intestinal flora and longevity and one of the important directions of future research on intestinal flora and longevity is to carry out

personalized regulation of intestinal flora on the basis of understanding the characteristics of intestinal flora. In addition, the study on the intestinal flora of the families of long-lived people can also further explore the influence of genetic factors on the intestinal flora.

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Effect of Metformin on Lactate Metabolism in Normal Hepatocytes under High Glucose Stress in Vitro

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ABSTRACT

To study the effect of metformin on lactate metabolism in hepatocytes in vitro under high glucose stress. Method: LO2 hepatocytes was cultured in vitro, hepatocytes were randomly divided into blank control group, 25 mmol/L glucose solution, 27 mmol/L glucose solution, 29 mmol/L glucose solution, 31 mmol/L glucose solution, 33 mmol/L glucose solution, 35 mmol/L glucose solution treatment group, after determining the optimal concentration as 31 mmol/L, use 30 mmol/L metformin solution, and then divided into blank control group, normal hepatocytes + the optimal concentration of glucose solution, normal hepatocytes + metformin solution, normal hepatocytes+. The optimal concentration of glucose solution normal hepatocytes + metformin solution, calculate the number of hepatocytes on cell count plate respectively in the 12 h, 24 h, 48 h, and use the lactic acid kit to determine the lactic acid value of the cell culture medium of normal liver cells + optimal concentration glucose solution and normal liver cells + optimal concentration glucose solution + metformin solution at 12 h, 24 h, and 48 h, respectively. Results: There was no significant change in the lactic acid concentration but significant increase in the number of surviving hepatocytes in the highglycemic control group compared with that in the highglycemic control group without metformin. Conclusions: Metformin has no significant effect on lactic acid metabolism of hepatocytes under high glucose stress in vitro, and has a protective effect on hepatocytes under high glucose stress. Based on this, it is preliminarily believed that metformin is not the direct factor leading to diabetic lactic acidosis.

Keywords:Metformin;Hepatocyte;Metformin associated lactic acidosis (MALA)

1.Introduction

With the change of people's lifestyle and habits, the incidence of diabetes is on the rise. At present ,1.01 million new diabetic patients are added every year in China. Of the 59 million people projected to reach 2025, more than 90

per cent are II diabetes (T2MD) . China has the largest number of diabetics. Because the development of diabetes involves many factors, the pathogenesis is more complex, and there is a variety of damage mechanisms interaction, can not be cured. Traditional antidiabetic drugs play

a good role in controlling blood glucose and delaying complications, but there are still some limitations and adverse reactions. Metformin is an oral antidiabetic drug of biguanidine. Because of its remarkable antidiabetic effect and clinical application value, metformin is widely used in clinic. Metformin is also regarded as the first-line anti-diabetic drug in the world. HOME and DDP experimental studies have demonstrated the safety and efficacy of metformin in the treatment of diabetes. However, with the increase of clinical application of metformin, some side effects have been gradually shown during its use as an antidiabetic drug, among which lactic acidosis (LA) is a concern of clinicians. Patients with lactic acidosis caused by taking metformin, is called as Metformin-related lactic acidosis (MALA), MALA is a rare and severe adverse reaction during metformin treatment because metformin hindered the pathway of lactic acid to glucose in mitochondria, causing Too much lactic acid produced or too little eliminated in the body, leading to metabolic disease, which has a very high mortality rate. Studies have shown that metformin-induced lactic acidosis may be associated with severe disease in diabetic patients themselves. It is mainly related to renal insufficiency, hypoxia and so on. Based on this, this paper will explain the effect of metformin on lactic acid metabolism in normal hepatocytes under in vitro high glucose stress, and then explore whether metformin has a direct correlation with lactic acid metabolism. To provide reference for clinical treatment of diabetes and the rational use of metformin.

2. Materials and Methods

2.1 Main Reagents and Instruments

Reagent: Cell selected LO2 hepatocyte strain, DMEM medium, trypsin, penicillin-streptomycin double antibody mixed solution, metformin, 10% fetal bovine serum, lactate assay kit (all purchased from Haikou Ruike Biotechnology Co., Ltd).

Instruments: Microscope, Ultra-clean Biological Table, CO2 Cell incubator.

2.2 Experimental Methods

2.2.1 Cell Culture

LO2 cells were used in a DMEM complete culture medium of 10% fetal bovine serum, Cultured in 37°C , 5% CO2 incubator. The culture box was cultured to the cell wall, and the conventional cell culture was changed once ~2 days. When the cell coverage reached 80% and 90%, take a transgenral culture, repeat operation. Freeze a bottle of subcultured cells to avoid accidental lack of LO2 hepatocytes.

2.2.2 A Comparative Experiment 1.2.2 Grouping Model

Establishment of high sugar model

High glucose pretreatment of LO2 hepatocytes was performed before the experiment, was performed (Glucose, G) the optimal concentration test, G concentration gradient is set as 0 mmol/L, 25 mmol/L, 27 mmol/L, 29mmol/L, 31 mmol/L, 33 mmol/L, 31 mmol/L calculated out as optimal experimental concentration, The lactic acid content was measured by lactic acid kit.

Establishment of the metformin model

Metformin hydrochloride tablets were diluted to 30 mmol/L to cell culture medium and pretreated LO2 hepatocytes for, the culture time

is 12 h, 24 h, 48 h.

Establishment of intervention model

The metformin hydrochloride medium with 30 mmol/L concentration and glucose solution with 31 mmol/L concentration were added to the culture bottle. After 12 h, 24 h, 48 h of culture, the lactic acid content was calculated by lactic acid kit.

2.2.3 Proliferation of Hepatocyte by Cell

Table 1. Optimal Sugar Concentration (Normal hepatocytes)

Concentration of glucose added (mmol/L)	25	27	29	31	33	35	0
12 h (surviving hepatocytes)	1.12×10 ⁷	1.06×10 ⁷	1.02×10 ⁷	0.98×10 ⁷	0.88×10 ⁷	0.40×10 ⁷	1.30×10 ⁷
13 h (surviving hepatocytes)	2.04×10 ⁷	1.97×10 ⁷	1.95×10 ⁷	1.92×10 ⁸	1.72×10 ⁸	1.25×10 ⁸	2.60×10 ⁷
14 h (surviving hepatocytes)	3.99×10 ⁷	3.92×10 ⁷	3.79×10 ⁹	3.76×10 ⁹	3.63×10 ⁹	3.19×10 ⁹	5.20×10 ⁷
15 h (surviving hepatocytes)	1.68 Soil 0.29	2.46 Soil 0.79	3.27 Soil 1.38	3.48 Soil 1.42	4.63 Soil 1.63	5.34 Soil 2.26	0
16 h (surviving hepatocytes)	3.89 Soil 1.42	4.79 Soil 1.68	5.24 Soil 2.17	5.89 Soil 2.64	6.23 Soil 2.79	8.98 Soil 2.86	0
17 h (surviving hepatocytes)	6.72 Soil 2.33	8.43 Soil 2.56	9.14 Soil 2.99	9.28 Soil 3.11	10.87 Soil 3.34	11.27 Soil 3.39	0

2.2.4 Hepatocyte Proliferation was Determined by Cell Counting Method

After adding metformin solution and high sugar treated cell solution into carbon dioxide cell incubator for 12 h, 24 h, 48 h, the lactic acid value in cell culture medium was determined by lactic acid kit, so as to judge the effect of dimethyl double strand on cells with high sugar.

2.3 Statistical Methods

The statistical analysis uses SPSS25.0 statistical software to process the data. The sample mean is used by sample t test, and the multiple mean is analyzed by single factor variance to. P<0.05 was statistically significant.

3. Results and Analysis

The G concentrations of the most suitable hepatocytes LO2 high glucose stress were explored after this experiment, as shown in Table

Count

The cells were decomposed by trypsin, digested for a period of time and then added to the culture medium to terminate the digestion. Then the culture medium was removed to the counting board with the liquid transfer gun, and the cells were counted strictly according to the rules of cell counting.

1, and the optimum experimental concentrations were obtained when the G concentration was 31 mmol/L.

The control group and experimental group were equipped with 30 mmol/L of metformin in culture medium. Normal hepatocytes, high glucose + normal hepatocytes, metformin + normal hepatocytes, high glucose and metformin + normal hepatocytes were designed respectively. The changes of lactate concentration measured in 12 h, 24 h, 48 h of culture were shown in Table 2.

Metformin itself does not produce lactic acid in hepatocytes. In high glucose environment, according to the experimental results of 2 and 4 groups, before metformin was added, The concentration of lactic acid in the culture medium of high glucose + normal hepatocytes increased from 1.42 mmol/L to 3.48

mmol/L, then increased to 5.89 mmol/L after 24 h, The increase rate of cell number began to decrease significantly after 48 h, lactic acid concentration also increased to 9.289 mmol/L. After metformin was added, there was no significant change in lactate concentration and cell number compared with those under high glucose stress.

4. Discussion

A large number of studies have shown that lactic acidosis is a rare and serious complication of diabetes, most of which occurs in patients with biguanidine and accompanied by liver and kidney insufficiency, heart failure and so on . Recent studies have found that the association of lactic acidosis (Metformin Lactate Acidosis, MALA) caused by metformin with a normal therapeutic dose is rare, but improper clinical use may also lead to elevated plasma

lactate levels and even lactic acidosis (Lactate Acidosis, LA).1. The liver is an important organ of glucose metabolism. The liver can absorb and use glucose, then reduce blood glucose and can convert glucose into liver glycogen and store it. Increased insulin resistance in cirrhotic patients affects glucose metabolism and causes hepatogenic diabetes. Diabetes also affects the liver, especially in patients with type 2 diabetes, and is prone to liver damage and nonalcoholic fatty liver disease. Metformin, as a traditional antidiabetic agent, can promote glucose metabolism, increase its anaerobic fermentation, increase the level of lactic acid and lead to lactic acidosis. In addition, metformin can inhibit the utilization of lactic acid by liver and muscle, inhibit gluconeogenesis, thus reducing glucose production, thus increasing the risk of lactic acid poisoning.

Table 2. Effects of metformin on lactate metabolism in normal hepatocytes under high glucose stress.

	Group 1 (normal hepatocytes)			Group 2(normal group + high glucose)		
	12h	24 h	48 h	12h	24 h	48 h
Concentration <u>mmol/L</u> of glucose added	/			31		
Add metformin concentration (<u>mmol/L</u>)	/			/		
Concentration of lactic acid (<u>mmol/L</u>)	0	0	0	3.48 Soil 1.42	5.89 Soil 2.64	9.28 Soil 3.11
Number of surviving hepatocytes (m)	1.30×10 ⁷	2.60×10 ⁷	5.20×10 ⁷	0.98×10 ⁷	1.92×10 ⁸	3.76×10 ⁹
	Group 3(normal group + metformin)			Group 4(hepatocyte + high glucose + metformin)		
	12h	24 h	48 h	12h	24 h	48 h
Concentration <u>mmol/L</u> of glucose added	/			31		
Add metformin concentration (<u>mmol/L</u>)	30			30		
Concentration of lactic acid (<u>mmol/L</u>)	0	0	0	3.30 Soil 1.39	5.83 Earth 2.63	9.17 Soil 3.08
Number of surviving hepatocytes (m)	1.30×10 ⁷	2.60×10 ⁷	5.20×10 ⁷	1.15×10 ⁷	2.24×10 ⁷	4.79×10 ⁷

In this study, metformin had little effect on lactate metabolism in hepatocytes in high glucose environment. After adding different levels of metformin to the experimental group and the control group, there was no significant difference in lactate content. However, different levels of metformin can promote cell proliferation. The high glucose environment can inhibit the proliferation of hepatocytes, which may be due to the STC2 expression induced by high glucose, and the overexpression of STC2 can further enhance the inhibition ability of hepatocyte proliferation induced by high glucose. Moreover, studies have shown that high glucose can promote the secretion of TNF- α , IL-6, and other inflammatory cytokines and regulate the expression of apoptosis-related molecules B lymphoma 2 and Bax, thus inducing hepatocyte apoptosis. Metformin can promote the proliferation of hepatocytes, probably because it can inhibit the secretion of inflammatory cytokines and the activity of nuclear transcription factor κ B (NF- κ B) through AMPK dependent pathway, so as to promote cell proliferation.

To sum up, metformin has no great effect on lactate metabolism in hepatocytes in high glucose environment, but different concentrations of metformin have protective mechanism on hepatocytes and can promote cell proliferation.

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Research and Prospect of Quality Development of Pharmaceutical Technology in Drug Research and Development

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ABSTRACT

Pharmaceutical technology is an indispensable and important link in drug research and development, which plays a key role in drug research and development quality. In the background of science and technology development, pharmaceutical technology has been greatly developed, but also to promote the quality of drug research and development, to provide more guarantee for people's health. In the new era, how to achieve pharmaceutical technology innovation, so as to further improve the quality of drug research and development, is an important research topic in the current related industries. This paper mainly revolves around quality of pharmaceutical technology development of a series of exploration, in the traditional drug development based on a better control of drug quality, the future of smart pharmaceutical green pharmaceutical development direction, aims to further enhance the pharmaceutical technology, promote the quality of research and development to promote the comprehensive, promote the steady development of the pharmaceutical industry as a whole.

Keywords:Drug research and development Pharmaceutical process;Quality development; Intelligent pharmaceutical;Green pharmaceutical

1.Introduction

With the gradual development of science and technology, more and more new technologies and new processes have been widely used in drug research and development, which further promotes the optimization and innovation of pharmaceutical process and injects new vitality into the stable development of the entire pharmaceutical industry. Strengthening the promotion and development of pharmaceutical technology can steadily improve the quality of drug research and development,

effectively control the drug cost and price, and promote the double improvement of economic benefits and social benefits. Therefore, the related industries should strengthen the in-depth research of pharmaceutical process, promote the innovation of process, and create a broader space for the development of pharmaceutical process.

2.Importance

2.1Promoting the Development Level of the Pharmaceutical Industry

With the gradual development of science and technology, drug research and development technology are improving day by day, which has produced great social benefits and brought great guarantee for human health. Different from other industries, the development of the medical industry is directly related to the life, health and safety of human beings, so as to ensure that people's body can get effective treatment. Through drug research and development, pharmaceutical technology development and quality improvement, to achieve reasonable control of drug prices. Through the reasonable control of drug prices, relieve the life pressure of patients' families, and truly take responsibility for human life and health.

2.2 Providing Better Drug Services

Drug development has certain risks, and the drug market access threshold is high, especially in the stage of new drug promotion, which makes pharmaceutical enterprises bear great market risks. Only on the basis of ensuring the efficacy of drugs, the pharmaceutical process is optimized and reformed, and the production cost is reasonably controlled, can the economic benefits of pharmaceutical enterprises be guaranteed, and better drug services can be provided for people. Therefore, it is necessary to carry out comprehensive reform and innovation on drug research and development and pharmaceutical process, promote the development level of pharmaceutical process, in order to truly guarantee the legitimate use of pharmaceutical enterprises, and lay the foundation for the long-term development of pharmaceutical enterprises. However, in this process, pharmaceutical enterprises should

correctly realize their social responsibilities, strictly check pharmaceutical materials and equipment, and avoid problems such as low-quality drugs or fake drugs.

3. Current Development Status of Traditional Drug R&D and Pharmaceutical Process Quality

3.1 Preparation Principle

The quality of raw materials and equipment is an important material basis for improving pharmaceutical quality. Many drug quality problems are caused by problems with raw materials and equipment. Therefore, the quality of pharmaceutical raw materials should be strictly checked. In order to reduce the cost, some pharmaceutical companies buy low-quality raw materials, which not only reduces the efficacy, but also may seriously threaten people's lives and health. In addition, it is necessary to pay attention to strict quality storage and maintenance of pharmaceutical equipment. In the purchase of equipment, to choose high-quality pharmaceutical equipment, in order to ensure that the quality of the drug guidance out of the standard. When many pharmaceutical enterprises purchase equipment, they do not pay attention to the detailed inspection of the equipment, resulting in the purchase of equipment can not meet the corresponding quality standards. And in the application of equipment, often in the production of different kinds of drugs, the use of the same equipment, cleaning is not sufficient, resulting in a great impact on the performance of the drug. In addition, many pharmaceutical enterprises do not pay attention to the maintenance and

maintenance of equipment, after use, there is no comprehensive equipment disinfection, resulting in equipment rust phenomenon; In addition, the equipment is not cleaned in time, resulting in the residual drug residue in the equipment, once mixed into other drugs, it is easy to have a serious impact on the drug performance.

3.2 Insufficient Personnel Quality

Pharmaceutical personnel are the direct operators of pharmaceutical technology, so their comprehensive quality has a direct impact on the quality of drug development. In the actual pharmaceutical process, some positions of staff lack of responsibility, the work of enterprise is not high, often muddle along, cannot be fully engaged in the pharmaceutical work, it is easy to cause human error, resulting in problems in the pharmaceutical process; In addition, some companies don't pay attention to the professional training of comprehensive pharmaceutical personnel, resulting in a lack of professional knowledge and professional skill, pharmaceutical personnel seriously affect the normative use of pharmaceutical process, lead to promote the pharmaceutical effects, even drug quality problems, etc., for the long-term development of the pharmaceutical industry is very adverse.

4. Drug Research and Development Pharmaceutical Process from Where to Improve the Quality

4.1 Focusing on the Preparation Principle of Drug Research and Development Technology

Drug research and development and production is a fine production activity, which requires a high level of research and

development technology and preparation principle. Different preparation methods and principles will obtain different research and development effects, which may be positive or negative. Therefore, in the specific implementation of the pharmaceutical process,

different preparation principles should be comprehensively analyzed to give full play to the advantages of each preparation principle and ensure the safety and effectiveness of the application of pharmaceutical process to the greatest extent. In addition, the latest science and technology and biotechnology should be combined to optimize and upgrade the preparation scheme, so as to reduce the environmental pollution damage caused by the pharmaceutical process as much as possible.

4.2 Improving the Pharmaceutical Process from the Perspective of Quality Control of Raw Materials and Equipment

Pharmaceutical raw materials and equipment are important material guarantee to ensure the quality of drug research and development. The quality of raw materials of drugs should be strictly controlled to ensure compliance with the standard requirements. Only in this way can the quality of drugs be guaranteed. Once there are quality problems in raw materials, it will lead to the inefficiency of the whole pharmaceutical engineering. In addition, strict quality control should be carried out on pharmaceutical equipment, and timely replacement and upgrading of equipment should be carried out to ensure compliance with pharmaceutical requirements. In addition, we should pay attention to the scientific and reasonable daily management of pharmaceutical

equipment, timely cleaning and disinfection after the completion of use, to prepare for the next pharmaceutical application, to prevent rust and cross-contamination of drugs.

4.3 Optimize the Pharmaceutical Process from The Aspect of Improving the Quality of Pharmaceutical Personnel

Pharmaceutical personnel are the direct operators of pharmaceutical technology, their comprehensive quality level has a key impact on pharmaceutical quality. At present, the responsibility of some pharmaceutical personnel is not strong, lack of professional pharmaceutical skills, resulting in the overall pharmaceutical quality can not be effectively improved. Therefore, it is necessary to strengthen the supervision and management of pharmaceutical personnel, improve the quality level of pharmaceutical personnel, combine the actual situation, regularly carry out professional skills training, such as inviting experts in relevant fields to give lectures, strengthen the sense of responsibility, make up for the lack of professional knowledge; In addition, centralized skill training should be actively carried out to improve the skill level of pharmaceutical personnel and ensure the normative operation of pharmaceutical process. Establish a scientific and reasonable assessment mechanism to strengthen the participation enthusiasm of pharmaceutical personnel; It is necessary to create good conditions to attract more high-quality pharmaceutical personnel to participate in the pharmaceutical industry, optimize the talent structure, strengthen work innovation, and inject new vitality into the quality development

of pharmaceutical process.

4.4 Strengthening Supervision and Administration

National regulatory authorities should give full play to their own functions, carry out comprehensive quality supervision and management of all links of the pharmaceutical process, promote the standardization and standard of the pharmaceutical process, so as to provide guarantee for the improvement of pharmaceutical quality. First, to the pharmaceutical raw materials and production equipment, such as the implementation of comprehensive inspection and testing, especially to the quality of raw materials and equipment disinfection link for strict supervision, to ensure the standardization of the work process; Second, to implement a comprehensive supervision of the pharmaceutical process, to ensure the pharmaceutical personnel's pharmaceutical qualifications, to have professional skills, to ensure the standardization of pharmaceutical operations, for illegal operations to give a severe warning; Third, in the pharmaceutical end link, we should pay attention to the sampling test of all drugs, to ensure that the quality of drugs meets the standard requirements, and to review its side effects. Only after all drugs meet the standard, can we be allowed to leave the factory for sale.[6]

5. The Future Development Direction and Expectation of New Pharmaceutical Technology

5.1 Internal Improvement of Chemical Pharmaceutical Process

With the gradual development of science and technology, chemical pharmaceutical technology has been rapidly developed and widely used. Under the background of science and technology development, continuous optimization and improvement of chemical pharmaceutical process should be carried out according to the actual needs of current social development, so as to promote the innovation of pharmaceutical process. Practice has proved that through the internal improvement and innovation of pharmaceutical process, not only can greatly reduce the cost of drug R&D and manufacturing, but also can promote the efficiency of pharmaceutical process, to meet the new needs of the current society for drug R&D. With the gradual development of the society, the realization of the internal improvement of the pharmaceutical process has gradually become an important development trend of the pharmaceutical industry, and with the continuous development of science and technology, its improvement ideas and approaches will be more and more broad, for the development of the pharmaceutical process to create a better prospect. Recently, China has introduced a membrane filtration technology, which is environmentally friendly and low energy consumption technology, and effectively reduces the pollution problem in the chemical and pharmaceutical process. However, the current production equipment has become a major problem in the development of drug research and development and pharmaceutical technology, because part of the equipment is difficult to meet the pharmaceutical standards. Therefore, it is necessary to actively introduce

advanced production equipment to create conditions for internal process improvement. It can be seen that the internal improvement of chemical pharmaceutical process effectively improves the quality of pharmaceutical process.

5.2 Gradual Development of Biotechnology and Pharmaceuticals

With the development of biotechnology research, it has gradually realized the comprehensive combination with the pharmaceutical field, and further expanded the research and development way and space in the pharmaceutical field. In the new era, people pay more and more attention to the development of biotechnology, and through in-depth research and development, bio- technology has provided a great help and convenience to the development of human society, but also provides a strong support to the pharmaceutical field. Although the biological process is developed from the traditional biological pharmaceutical technology, there are many differences with the traditional pharmaceutical methods, which is both an inheritance and an innovation, and has made a great contribution to the development of the quality of the pharmaceutical process. At present, countries all over the world have strengthened the research and development of biotechnology, and further deepened the integration of biotechnology and pharmaceutical technology.

5.3 Green Pharmaceutical Technology Is Gradually Flourishing

In the new era, with the gradual deepening of the concept of green environmental protection, the application of drug research and development and pharmaceutical technology

has also gradually reflected the need for green environmental protection. The development of green technology has promoted the healthy and positive development direction of the pharmaceutical industry. The intelligent preparation process has realized the gradual transformation from chemical pharmaceutical to green pharmaceutical, reduced pollution and energy consumption, and truly reflected the healthy development direction of the quality of pharmaceutical technology of drug research and development.

6. Conclusion

Study of pharmaceutical research process quality need long-term persistence and efforts, relevant personnel to related problems to conduct a comprehensive analysis of the pharmaceutical technology, and pharmaceutical process each link to conduct a comprehensive innovation and optimization, especially the pharmaceutical raw materials, equipment and R&D staff strict quality control, create good basic conditions for the development of pharmaceutical technology. In addition, it is necessary to combine the development of science and technology, promote the internal improvement of pharmaceutical process, strengthen the full integration with biotechnology, and develop green pharmaceuticals such as intelligent pharmaceuticals in the future, so as to create new development directions for the development of pharmaceutical process, expand development space, and provide a solid foundation for improving the quality of drug research and development. Through the research on the development of drug research and development

and pharmaceutical technology, it can effectively improve the pharmaceutical efficiency, reduce the cost, reduce the price of drugs, produce good social benefits, but also provide guarantee for the comprehensive benefits of pharmaceutical enterprises.

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