2024.3
ISSN 3007-0090

Journal of General Practice Research and Translation

ISSN 3007-0090
9 773007 009000 >

Research Advance on the Relationship between Wee1 and Tumor Genesis and Progression

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ABSTRACT

In the process of biological genetic information transmission, complete and correct genetic information can make cell mitosis proceed normally. In the development of most tumor cells, G2/ M cell cycle checkpoint becomes the key checkpoint in the process of mitosis due to the lack of G1/ S cell cycle checkpoint, which mainly depends on the abnormal DNA information blocked by Wee1 protein kinase in G2 phase to enter M phase and prolong the time of G2 phase to complete DNA sequencing So that the normal genetic information can be passed on. Wee1 protein kinase expression is significantly increased in most tumor cells, making it a potential target for tumor therapy.

Keywords: Wee1 protein kinase;Cell cycle;Wee1 kinase inhibitor;Tumor

1.Introduction

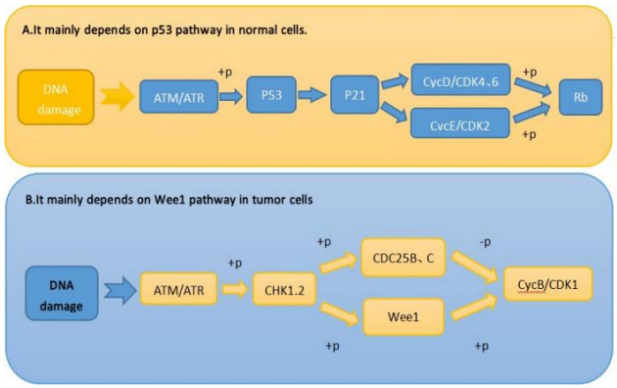
Wee1 protein kinase family includes Wee1A, Wee1B and Myt1 members. The human Wee1 gene is located in the P15 region of chromosome 15 (11p15.3-11p15.1), encoding 647 amino acids. Wee1 protein kinase consists of three domains: N-terminal domain, central kinase domain and C-terminal regulatory domain. The N-terminal domain is the activation domain of Wee1 protein kinase, which plays a key role in guiding its destruction, and may inhibit the activity of Wee1 protein kinase. However, the N-terminal domain is also a potential site for inhibiting CyCB/CDK1 dephosphorylation, thus causing cell cycle arrest. The central kinase domain is helpful for Wee1 localization in the nucleus at G2 phase; The C-terminal regulatory domain is the Wee1 protein kinase catalytic domain. Studies have shown that Wee1 is mainly expressed in the nucleus of tumor cells. In recent years, the research of Wee1 protein kinase in DNA repair of cell cycle damage and malignant tumors has become a hot spot. In normal cells, due to the existence of P53, cells can complete the damage repair in G1/S phase when DNA is damaged. However, the mutation of P53 occurs in most malignant tumors, resulting in that the damaged DNA can not be repaired in G1/S phase, and can only be repaired in G2/M phase, so that the correct and complete DNA can enter into M phase for mitosis. In this paper, the research progress of the relationship between Wee1 and tumor genesis and development is summarized

as follows.

2.Role of Wee1 Protein Kinase in Cell Cycle

Cell cycle is a concept proposed by Howard et al in 1951. It refers to the whole process of a cell from the completion of one division to the end of the next division, which is divided into two stages: interphase and division phase. The interphase is divided into G1, S and G2 phases, and the division phase is M phase. In the process of cell proliferation, cell mitosis will encounter a variety of damage factors causing DNA damage and chromosome variation, so someone put forward the concept of cell cycle checkpoint, namely a kind of negative feedback regulation mechanism, which is mainly affected by DNA replication and damage. There are two key checkpoints: G1/S and G2/M phases,which block the heredity of genes with replication errors. In normal cells, DNA damage mainly depends on two pathways mediated by P53(tumor suppressor gene): ATM(Capillary ataxia mutant gene)/ATR-P53-CDK4/CyclinD or ATM/ATR- P53-CDK2/CyclinE inhibit Rb phosphorylation, and make the cell arrest in the G1 phase to complete DNA damage repair. However, studies have shown that most tumor cells lack two pathways in the G1/S phase check- point, which makes the DNA damage repair of tumor cells mainly depend on the G2/M phase. Studies have shown that Wee1 and CDC25 play an important role in this checkpoint. ATM/ATR is activated when DNA damage, through the phosphorylation of downstream CHK1/2(effect kinase) make its activation. On the one hand, activated CHK1 / 2 can phosphorylate downstream CDC25B/C to inactivate it, inhibit its dephosphorylation of downstream CDK1/CycB, and arrest cell cycle in G2 phase. On the other hand, CHK1/2 can directly activate Wee1 protein kinase. The activated Wee1 protein kinase phosphorylates the thy15 site of CDK1 and inactivates it, which is the key factor for mitosis. The cell cycle is arrested in G2 phase until DNA damage repair is completed. The cell has the opportunity to enter M phase for mitosis. Wee1 protein kinase, as a potential molecular target of tumor cells, has become a focus of current research.

As shown in Figure 1：Figure 1. damage and repair process of G2 phase cells



3.Relationship between Wee1 Protein Kinase and Tumor

3.1Wee1 and Gastric Cancer

Gastric cancer is one of the most common malignant tumors in China. Many chemotherapy drugs can cause DNA damage in gastric cancer tumor cells. Tumor cells lack G1/S phase and most of them rely on G2 phase arrest. Wee1 is a key factor of G2/M checkpoint. Kim et al.first proposed that Wee1 protein kinase might be ex- pressed in gastric cancer. After a series

of experiments, it was found that Wee1 was positive in gastric cancer cells, and the positive rate was higher in tumor cells with lymph node metastasis, and the proliferation and invasion ability of tumor cells with Wee1 overexpression was stronger. Zhang et al.also verified that the expression of Wee1 was increased in gastric cancer cells, and fur- ther demonstrated that ROP inhibited the proliferation and metastasis of gastric cancer cells by regulating the Wee1 pathway.

3.2Wee1 and Melanoma

In malignant melanoma, regardless of the status of P53, the high expression of Wee1 can reduce the DNA damage of tumor cells, and is positively correlated with the proliferation, metastasis and poor prognosis of malignant melanoma. Studies have shown that, different from most tumors, P53 expression is positive in malignant melanoma. Wee1 is a key signal molecule downstream of BRAF in MAPK signal transduction pathway. Wee1 can inhibit the P53-P21-CDK2/CycE- Rb-E2F pathway in the cell cycle, so that the cell cycle is blocked in the S phase, therefore, the expression of Wee1 protein kinase is still positive in melanoma. Wee1, as the most suitable target, its inhibitor and AKT3 pro- tein kinase inhibitor combined to treat melanoma, so that the treatment effect of AKT3 inhibitor is more effective. In animal experiments, high expression of Wee1 and deletion of MicroRNA-155 (MiR-155) contribute to metastasis of malignant melanoma. However, Bhattacharya et al.showed that compared with primary melanoma, the expression of Wee1 in distant skin metastatic melanoma was down regulated, and the proliferation, migration and invasion ability of Wee1 positive primary tumor cells were decreased.

3.3Wee1 and Colorectal Cancer

Wee1 can be expressed in both colon cancer tissues and paracancerous normal tissues, but it is highly expressed in colorectal cancer. Experiments showed that the expression of Wee1 is mainly positive in the nucleus, but also slightly expressed in the cytoplasm, and the high expression of Wee1 is closely related to distant metastasis of colon cancer, lymph node metastasis and malignant degree of tumor. Yin et al.verified that Wee1 inhibition can reduce the proliferation ability of tumor cells in P53 mutated colorectal cancer, and Wee1 may become a potential target for the treatment of colorectal cancer. Webster et al. also found that the positive expression rate of Wee1 was up-regulated in endothelial cells with liver metastasis from colorectal cancer, and Wee1 may be related to the formation of some branches of blood vessels in liver metastasis from colorectal cancer, which provides a theoretical basis for the research and development of Wee1 protein kinase inhibitors as tumor drugs.

3.4Wee1 and Breast Cancer

Triple Negative Breast Cancers (TNBCs) are breast cancers that are negative for estrogen receptors, progesterone receptors and human epidermal growth factor receptors. Studies have found that p53 mutations in the vast majority of TNBCs lead to deletion of G1/S stage checkpoints, making Triple Negative Breast Cancer dependent on G2/M stage checkpoints to repair DNA damage. Experimental results showed that Wee1 inhibitor combined with

ATR inhibitor can inhibit proliferation and metastasis of TNBCs and induce apoptosis of cancer cells. Ghiasi et al. eliminated G2 phase arrest, accumulated P53, increased G1 phase arrest and significantly reduced the expression of pro-tumor vascular growth factor VEGF by inhibiting Wee1, thus weakening the proliferation ability of cancer cells, indicating the cancer-promoting effect of high expression of Wee1 in breast cancer cells.

3.5Wee1 and Lung Cancer

Yoshida et al. analyzed 79 patients by immuno- histochemistry, including 16 recurrent cases, and found that there was almost no difference in the positive rate of Wee1 between tumor cells and normal cells. Moreover, the recurrence rate and mortality of patients with Non- Small Cell Carcinoma(NSCLC) with negative Wee1 expression were significantly higher than those with positive Wee1 expression. These results suggest that Wee1 expression may act as a protective mechanism against cancer in NSCLC. However, Ku et al.proved that Wee1 protein kinase inhibitor was effective in the treatment of non-small cell lung cancer with KARs gene mutation in TP53 mutated cancer cells, which was similar to the effect of Wee1 inhibitor combined with mTOB inhibitor in the treatment of NSCLC with KARs gene mutation studied by Hai et al. Jhuraney et al. found that Wee1 and PAXIP1 were commonly expressed in lung cancer,and had no relationship with the status of p53. When both were expressed at the same time, Wee1 inhibitor combined with Cisplatin was effective.Sen et al. a used PCR method to study and found that Wee1 was significantly increased in small cell lung cancer cells compared with normal tissues and non-small cell lung cancer cell lines. Therefore, the mechanism and expression of Wee1 may be different in different types of lung cancer.

3.6Wee1 and Lymphoma

Lymphoma is a malignant tumor originated from lym- phohematopoietic system, which is a systemic disease. At present, the main treatment is chemotherapy, but lymphoma is heterogeneous, and the therapeutic effect is different greatly among different patients. Chemotherapy drugs such as cytarabine can cause DNA damage in B-cell lymphoma. The results showed that in vivo and in vitro, Wee1 inhibitor combined with chemotherapy drugs was only effective in the treatment of B-cell lymphoma with G2 phase arrest. Diffuse large B-cell lymphoma (DLBCL) accounts for about 31% of all non Hodgkin's lymphoma. Although R-CHOP Regimen is more effective, there are still a lot of relapses or deaths.Studies have shown that Wee1 is more significantly expressed in DLBCL. Wee1 inhibitors combined with CDK1 inhibitors may improve the prognosis of patients with DLBCL, and Wee1 may become a target for the treatment of Diffuse Large B-cell Lymphoma. De Jong et al. first proposed and verified that Wee1 inhibitor can enhance the anti-apoptotic depen- dence of DLBCL, and the combination of Wee1 inhibitor and anti-apoptotic inhibitor has better efficacy. Chila et al.demonstrated that CDK1 inhibitors and Wee1 inhibitors were more effective in Mantle Cell Lymphoma (MCL) than solid tumors and other lymphomas, but the high toxic side effects of dual-targeted agents remain to be addressed.

4.Wee1 Protein Kinase Inhibitors

Among tumor therapy drugs, targeted therapy drugs have been widely used in clinic. In recent years, Wee1 protein kinase has attracted more and more attention in tumor cells with G1/S checkpoint deletion, and Wee1 protein kinase plays a key role in G2/M phase, making Wee1 protein kinase become a potential target for clinical treatment of tumors. Wee1 protein kinase inhibitor AZD1775, also known as MK1775, is an effective selective inhibitor of Wee1. AZD1775 can inhibit the activity of CDK1 by phosphorylating the Try15 residue of Wee1 protein kinase, so that DNA damage repair can not be carried out smoothly, and cells can not produce substances entering M phase in G2 phase, which leads to apoptosis. Studies have proved that AZD1775 alone is effective in the treatment of tumors. Currently, the treatment methods for patients with ovarian cancer are not perfect. Zhang et al.verified through animal experiments that Wee1 inhibitor MK1775 as a single preparation has an inhibitory effect on tumor cells of ovarian cancer, and Wee1 may become a potential target of ovarian cancer. Bi et al. determined that the expression of Wee1 was increased in esophageal squamous cell carcinoma cells, and thus verified that AZD1775 alone could inhibit the proliferation and metastasis of cancer cells and induce their apoptosis. Jin et al. found that Wee1 inhibitor AZD1775 can block mitosis in S phase in pancreatic cancer, and make the cells in this phase be inhibited and apoptosis, so as to achieve the effect of treating pancreatic cancer.In recent years, Acute Lymphoblastic Leukemia (ALL) treatment drugs have made patients get very effective treatment effect, but tumor recurrence has become a problem perplexing patients and doctors. It has been proved that AZD1775 combined with CHK1/CHK2 inhibitor can act in S phase to make DNA damage and achieve therapeutic effect on patients with ALL. Junchenghu et al. found that T-ALL was more dependent on G2/M phase in DNA damage due to the lack of G1/S phase, making Wee1 a key therapeutic target. The experimental results showed that Wee1 was closely related to the glycolysis of cells, which verified that Wee1 inhibitor AZD1775 combined with GLS1 inhibitor CB-839 and BPTES had better efficacy in the treatment of T-ALL than using the two drugs alone. According to Cody W. Lewis et al. the presence of Myt1 in the cell cycle can phosphorylate the Thy14 site of CDK1, and also block the mitosis of cells, which can enhance the drug resistance of some tumors such as breast cancer to AZD1775. Therefore, the combined application of Wee1 inhibitor and Myt1 inhibitor in the treatment of some tumors may reduce the resistance of tumor cells to Wee1 inhibitor.

Other studies have demonstrated that Wee1 inhibitors will appear drug toxicity and drug resistance when used alone or in combination with other drugs to treat tumors, while Wee1 inhibitors will have better efficacy and fewer side effects when used continuously with other anti-tumor drugs. Yongfang et al. showed that nausea, weight loss and other symptoms could occur when Wee1 inhibitors were combined with PARP inhibitors, while continuous use of the two drugs alone could not only kill tumor cells,

but also improve toxicity in normal cells. There have also been studies showing that sequential therapy with gemcitabine followed by Wee1 inhibitor can increase the number of tumor cell apoptosis more than alternating sequential therapy with gemcitabine followed by Wee1 inhibitor or combination therapy of gemcitabine and Wee1 inhibitor.

5.Summary

In this review, the role of Wee1 protein kinase in the cell cycle and the relationship between Wee1 protein kinase and tumor were summarized, and the development of Wee1 protein kinase inhibitors in tumor therapy was summarized. Wee1 protein kinase inhibitors are potentially targeted tumor therapy drugs. Currently, there are many researches on Wee1 inhibitors, but how to use Wee1 inhibitors to minimize the toxic and side effects of the treatment regimen is still controversial: Some scholars believe that single use is more effective than combined use; some scholars believe that combined use can reduce the side effects caused by Wee1 inhibitors, and combined use can maximize the efficacy; while others believe that neither single use nor combined use can bring the maximum benefit to patients as sequential therapy. As Wee1 protein kinase inhibitors are still in phase II clinical trials, how to keep the efficacy of the drug itself, and at the same time control the balance be- tween Wee1 protein kinase inhibitors and other drugs or treatments to bring the greatest benefits to patients is the current research direction.

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Evaluation of Light Specific Gravity Ropivacaine Combined with Sufentanil in Hip Arthroplasty at An Advanced Ager

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ABSTRACT

Objective: To observe the effect of light specific gravity ropivacaine combined with sufentanil in elderly patients undergoing hip replacement. Methods: 89 elderly patients with hip arthroplasty from July 2019 to September 2020 were randomly divided into experimental group and control group. The experimental group was anesthetized with light specific gravity ropivacaine combined with sufentanil. The control group was anesthetized with equal specific gravity ropivacaine to compare the effect of anesthesia and the incidence of adverse reactions. Results: there was no significant difference in sensory recovery time and motor recovery time between the experimental group and the control group (P>0.05), and the incidence of adverse reactions between the two groups was low. The sensory block time in the experimental group was shorter than that in the control group (PP>0.05). Conclusion: ropivacaine combined with sufentanil subarachnoid anesthesia is more effective in elderly patients undergoing hip arthroplasty, and the safety of the anesthesia scheme is higher, which will not lead to serious adverse reactions during operation. Moreover, the application of the anesthesia scheme can effectively improve the analgesic effect during and after operation, and the clinical application value is high.

Keywords: Light specific gravity ropivacaine;Sufentanil;Elderly patients;Hip replacement;Safety

1.Introduction

With the increase of age, the body function of the elderly gradually decreased, bone mineral density and bone mass decreased significantly when they were younger, and the probability of orthopedic diseases was very high. Clinically, surgery is a common treatment method for patients with complex orthopedic diseases. The reduction and fixation of broken bones by surgical incision is helpful to relieve pain symptoms and reduce the occurrence of complications. It is of great significance to improve the quality of life of orthopedic patients. Hip replacement is a common operation in orthopedic field. Hip replacement is often needed in elderly patients with femoral neck fracture. In the course of surgical treatment, high quality anesthesia is essential, but anesthesia may lead to hemodynamic fluctuations and anesthetic risks, so safe and

effective anesthesia is essential. There- fore, this paper studies the clinical anesthesia of elderly patients with hip arthroplasty, and compares the effect of different anesthesia schemes.

2.Information and Methodology

2.1General Information

This study has been submitted to the ethics committee of our hospital and approved, The 89 elderly patients who underwent hip arthroplasty in our hospital from July 2019 to September 2020 were randomly divided into experimental group (n=45 cases) and control group (n=44 cases) by drawing lots, All subjects were not treated with analgesic drugs within 3 d before the start of the study, And sign informed consent, excluding those with combined cognitive dysfunction. In the experimental group, 23 males and 22 females; Age range 68-79, median age (73.24±2.67) years, Among them ,11 patients with hypertension and 13 patients with diabetes. In the control group, 22 males and 22 females; Age range 67-79, median age (73.37±2.66) years, Among them, 9 patients with hypertension and 12 patients with diabetes. General data of sex and age of experimental group and control group were verified by statistical software P>0.05, Comparable.

2.2Method

2.2.1Drugs

Ropivacaine: Shijiazhuang four Medicines Co.,Ltd.,100 mg. H20203107, specifications

Sufentanil: Yichang Renfu Pharmaceutical Co., Ltd.Production, H20054171, specifications 50μg.

2.2.2Anesthesia Process

Both groups were given routine perioperative nursing, preoperative examination and routine monitoring of vital signs after entering the operating room. The L3-4 of healthy lateral position or L2-3 spinous process space was selected as the puncture point during anesthesia, and the corresponding anesthetic drugs were injected according to the difference of patient group after the successful combination of lumbar and hard puncture. Subarachnoid injection of 10 mg ropivacaine into 3 ml light specific gravity solution combined with sufentanil (2.5μg) was performed in the experimental group. The time of administration was 30s; and the control group was anesthetized with equal specific gravity ropivacaine 15 mg. The time of administration was 30s. 5min, 10min, 15min after anesthesia, the anesthetic effect and the anesthetic plane were tested respectively. After the effect reached the requirement of operation, the patient's position was adjusted and the subsequent operation was carried out.

2.3Assessment Criteria

The difference of anesthetic effect and adverse reaction rate between experimental group and control group was verified by statistical software.

Anaesthesia: Sensory block time (test the sensory block plane with a cotton swab, A sensory block time (1-3 points) and an intraoperative analgesia score (T12) were recorded when the affected sensory block plane reached, One point indicates obvious discomfort or pain during the operation, Need intravenous sedation or analgesic drugs for adjuvant treatment; Two points indicate slight discomfort

or pain during the operation, but without medication; 3 points indicate no discomfort or pain during operation, sensory recovery time (after injection of anesthetics to complete recovery time of lower limb sensation), motor recovery time (after injection of anesthetics to complete recovery time of lower limb movement), postoperative analgesia score (according to the patient's postoperative self-controlled analgesic pump and other anesthetic use of score assessment, Ten points, After the operation, the patient used a self-controlled analgesic pump deduction of 0.1 points, Deduct 1 point for each additional use of other analgesic drugs)[1].

Adverse reactions: hypotension, bradycardia, shivering, nausea and vomiting.

2.4 Statistical Methods

The SPSS 24.0 software was used to compare the difference of observation indexes between groups, the counting index was expressed by n(%), and the measurement index was expressed by (x±s). If the P value is less than 0.05, the difference between groups is meaningful.

3.Fruit

3.1Differences in Anesthetic Effect between Experimental and Control Groups

Table 1 showed that there was no significant difference in sensory recovery time and motor recovery time between the experimental group and the control group (P>0.05), and the sensory block time in the experimental group was shorter than that in the control group, while the intraoperative analgesia score and postoperative analgesia score were higher than those in the control group (P>0.05).

Table 1. Differences in anesthetic effect between experimental group and control group (x±s)`

Group	n	Duration of sensory block (min)	Intraoperative analgesia score (score)	Feeling recovery time (min)	Exercise recovery time (min)	Postoperative analgesia score (score)
Experimental group	45	12.86±2.68	2.36±0.44	321.52±44.87	207.35±28.39	9.39±0.47
Control group	44	16.35±2.57	2.07±0.51	316.82±57.62	209.47±37.61	7.82±0.85
t	-	6.2681	2.8743	0.4299	0.3006	10.8152
p	-	0.0000	0.0051	0.6683	0.7645	0.0000

Table 2. Differences in the incidence of adverse reactions between experimental and control groups [n(%)]

Group	n	Low blood pressure	bradycardia	Cold War	Nausea and von
ıental group	45	0 (0.00)	2(4.44)	1(2.22)	2(2.22)
rol group	44	6(13.64)	1(2.27)	8(18.18)	1(2.27)
X2	-	4.5897	0.0004	4.6018	0.0004
p	-	0.0322	0.9842	0.0319	0.9842

3.2Differences in the Incidence of Adverse Reactions between Experimental and Control Groups

Table 2 shows that the incidence of hypotension and shivering in the experimental group was lower than that in the control group, and the difference between the two groups was statistically significant, $P<0.05$.

4.Discussion

In the treatment of hip replacement in elderly patients with orthopaedic diseases, Quality intraoperative anesthesia is indispensable, Good surgical anesthesia can not only promote the smooth operation of patients, it also reduces surgical stress, It is helpful to improve the effect of post- operative recovery. This study found that, Experimental group with light specific gravity ropivacaine combined with sufentanil had shorter sensory block time than control group with equal specific gravity ropivacaine anesthesia ($P<0.05$), And the intraoperative pain score and postoperative pain score in the experimental group were also higher than those in the control group ($P<0.05$), between groups, there was no significant difference in sensory recovery time, motor recovery time and incidence of adverse reactions ($P>0.05$). The results demonstrate the high-quality effect of light specific gravity ropivacaine combined with sufentanil in elderly patients with hip arthroplasty. The reason for the results is that ropivacaine is a commonly used anesthetic, it has the advantages of good anesthetic effect, long aging and less adverse reactions. But sufentanil, as an analgesic, has the advantage of quick action, Although the duration is short, the analgesic and sedative effects are obvious, Therefore, the intraoperative pain score and postoperative pain score of the experimental group were higher. And, Application of light specific gravity ropivacaine combined with sufentanil, can reduce the patient's posture changes caused by blood pressure fluctuations. The range of light specific gravity ropivacaine block is narrower than that of equal specific gravity ropivacaine, further reduce the incidence of hypotension, hypo- thermia. High incidence of shivering after anesthesia in elderly patients, Shivering can lead to increased oxygen consumption, energy consumption, can induce the old patient coexisting cardiopulmonary basic disease, Increase intraoperative risk and postoperative complications [6-8]. Addition of opioid analgesics, sufentanil, can provide perfect intraoperative analgesia, Reduce the incidence of shivering among patients, clearly reduce the of oxygen consumption and energy consumption caused by shivering. The postoperative analgesia is accurate, compared with the control group, the experimental group was more likely to stand on the ground the next day. Early getting out of bed in elderly patients can reduce postoperative complications due to bed rest, such as pulmonary infection, thrombosis, muscle atrophy and other. In the study of Geng Sujuan scholars, Ropivacaine alone reduces the duration of sensory block, But the combination of sufentanil can significantly improve the blocking effect, it helps to prolong the time of anesthesia and the effect of analgesia, and high security, Patients do not have severe adverse reaction. The results of this study are basically consistent with the contents of this study, to further prove the good

effect of ropivacaine combined with sufentanil subarachnoid anesthesia in the treatment of hip arthroplasty in elderly patients with orthopedic diseases, it is suggested that it can be used as an ideal anesthetic scheme in the treatment of elderly patients.

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In vitro Activity of Novel Cannabinoids Derived from Tetrahydrocannabinolic Acid on Various Human Tumor Cell Lines

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ABSTRACT

The in vitro study of tetracannabinolic acid (THCA) derivatives ALAM027 and ALAM108 was carried out on the following human tumor cells: T47D (breast, ductal carcinoma), PC-3 (prostate, adenocarcinoma), HT-29 (colorectal carcinoma), Caco-2 (colon, adenocarcinoma), A549 (lung,carcinoma), U87MG (human glioblastoma) and U266B1 (multiple myeloma).The in vitro effects of THCA derivatives ALAM027 and ALAM108 on cell growth inhibition and IC50 values were measured using the CellTiter Glo assay.The ALAM027 compound showed good growth inhibition in all cell lines tested with the exception of U87MG cells. The ALAM108 compound also suppressed the growth of U87 MG cells but had little effect on T47D tumor cells.In vitro studies of THCA derivatives ALAM027 and ALAM108 showed antitumor activity in all cell lines tested. The difference in the activity of these compounds in relation to the T47D and U87MG tumor cells may be indicative of different functional mechanisms.

Keywords:THCA;Cannabinoids;T47D;PC-3 HT-29;Caco-2;A549;U87MG;U266B

1.Introduction

Tetrahydrocannabinolic acid (THCA) is the main component of Cannabis sativa. However, in contrast to its derivative THC, the biological properties of THCA have been studied to a much lesser extent, particularly because it is difficult to isolate and because of its high sensitivity to heat and UV radiation. A convenient and inexpensive method has recently been described to isolate this acid using ion-exchange resins, opening up the way to industrial scale production and making THCA a suitable starting product for drug synthesis. This advance has recently facilitated the synthesis of two THCA derivatives, ALAM027 and ALAM108, which exhibit good anti-tumor-activity in PANC-1 and AsPC-1 cell lines.Since natural cannabinoids such as THC and CBD are known to have broad-spectrum anti-tumor activity against many types of tumors, it is of interest to investigate a potential effect of ALAM027 and ALAM108 on various types of cancer cells. According to World Health Organization data the most widespread types of cancers are breast, lung, colon, intestine, pancreatic, prostate tumors and blood diseases such as multiple myeloma. Brain tumors such as gliomas are also potentially interesting, particularly because of their aggressive and highly invasive properties.

To facilitate comparisons between previously

reported activities of natural cannabinoids and the ALAM027 and ALAM108 compounds, the current study examines the effects of these compounds on the following human cancer cell lines: T47D (breast, ductal carcinoma), PC-3 (prostate, adenocarcinoma), HT-29 (colorectal car- cinoma), Caco-2 (colon, adenocarcinoma), A549 (lung, carcinoma), U87MG (human glioblastoma) and U266B1(- multiple myeloma).

All these tumor cell lines express significant levels of CB1 and CB2 receptors in their cell membrane and this amount increases with cell proliferation. Thus, several articles have been devoted to studying the effects of THC and CBD on tumor cell line T47D which is often used in breast cancer research.

The PC-3 cell line is also often used in prostate cancer research. Studies examining the effects of cannabinoids on PC-3 cells have predominantly focused on elucidating tumor

growth suppression mechanisms.

The HT-29 cell line is a colorectal tumor line which is often used as an epithelial cell model to study new drug candidates because of its ability to differentiate. Cannabinoids have a significant effect on HT-29 cells as they induce cell death through apoptosis and inhibit proliferation. The role of cannabinoid receptors in these processes has been studied by examining effects of agonists such as THC and CBD on cancer cells in the presence and absence of CB1 and CB2 antagonists.

Similarly to HT-29 cells, natural cannabinoids also sup- press colorectal adenocarcinoma Caco-2 cell growth by inducing apoptosis and inhibiting cell proliferation which is mediated through CB1 receptor binding.

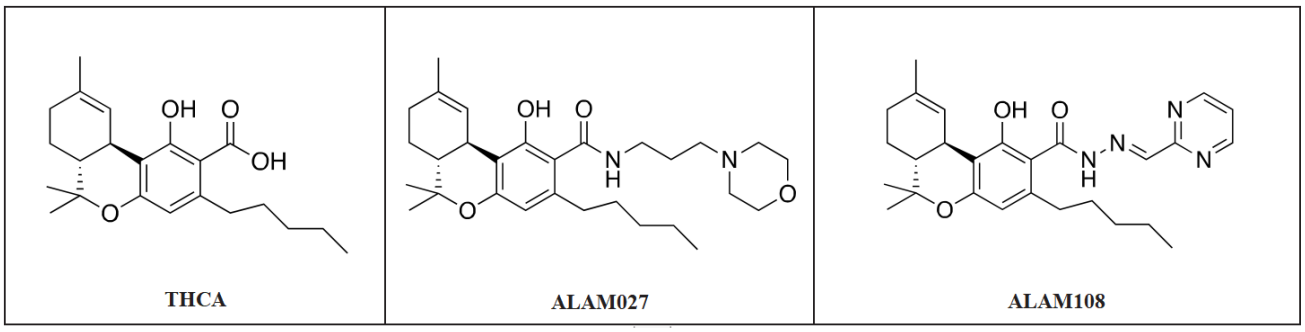
A549 is one of the most widely studied lung tumor cell line, which is often used as a testing ground for new drugs, such as natural and synthetic cannabinoids because the main determining factor of the anticancer effect of these cannabinoids on A549 cells is their ability to block the CB1 receptor, which is overexpressed in non-small cell lung tumors.

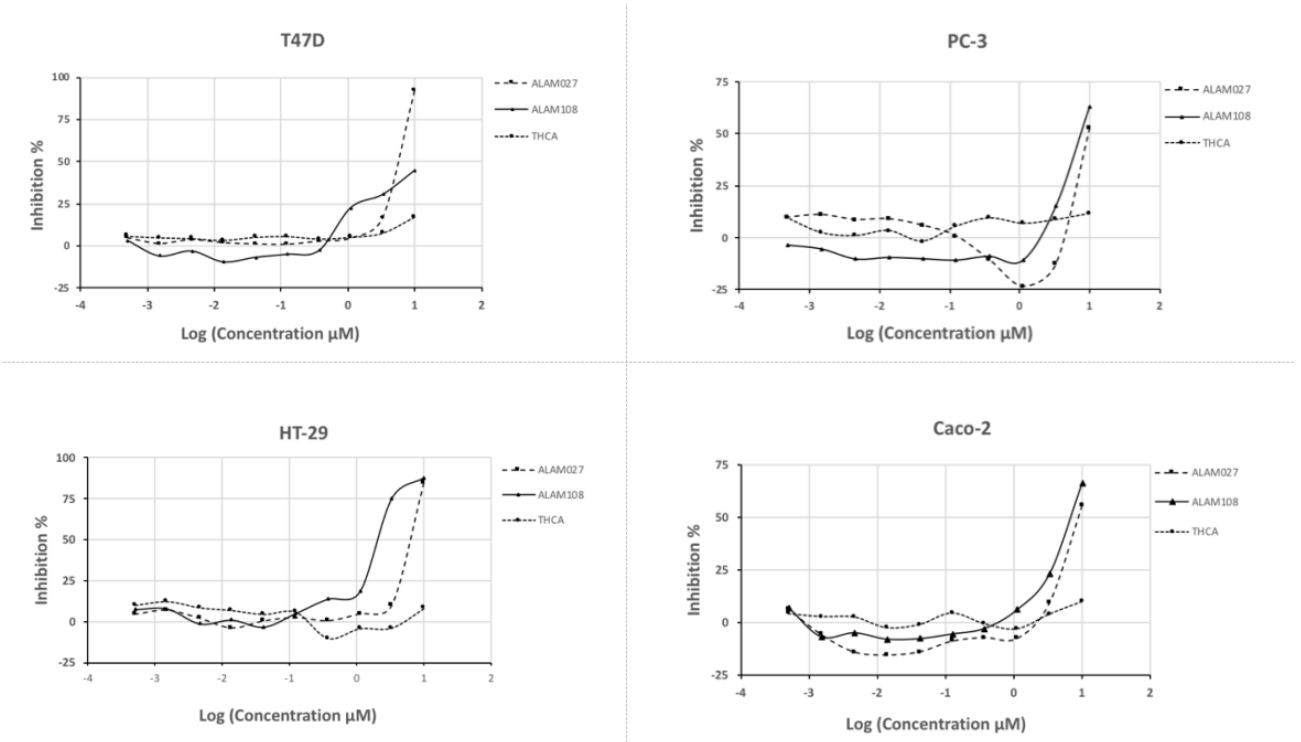
Brain glioblastoma occupies an important place among studies of the anticancer activity of cannabinoids. A significant number of research studies have focused on the effects of THC and CBD ligands on U87 MG, in particular because of their rather substantial in vitro and in vivo activities. It is interesting to note that, in contrast to SF126 glioblastoma cells, in the case of U87MG cells THC does not exhibit a pleiotropic effect at 1 μM concentration and below. Multiple myeloma is one of the most serious hematological diseases and is characterized by drug resistance. Cannabinoids are among the most promising candidates for the treatment of this disease. Recent research indicates that the IC50 values for CBD and THC in U266 cells are 19.8 μM and 39.5 μM respectively, and their combined use leads to the synergistic increase of cytotoxic effects when compared to their individual activities.

The present activity study of the ALAM027 and ALAM108 compounds in these selected tumor cell lines will not only allow to assess their anticancer activity but also, to a certain extent, could be used to understand their putative functional mechanisms.

2.Materials and Methods

Synthesis data and spectral characteristics of THCA derivatives ALAM027 and ALAM108 have been described previously. The in vitro study was performed on T47D, PC-3, HT-29, Caco-2, A549, U87MG and U266B1 cells obtained from the Chempartner (China) collection using the CellTiter Glo Viability Assay. Cells were seeded in 96- well plates in a volume of 100 µl per well, according to the planned plate layout and a predefined seeding density. Plates were incubated in a CO2 incubator overnight. The compound stock solution was diluted with DMSO to a 200 final concentration, and serial 3-fold dilutions prepared from a 2-mM solution (final concentration range: 0.5- 10000 nM for 10 doses). An internal staurosporine control was included on each plate. A volume of 0.5 µl of diluted compound was added to appropriate wells according to the plate layout. The plates were incubated at 5% CO2, 37°C for 72 hours. After this incubation, CellTiter-Glo reagents were prepared and added, and the plates read in an Envision plate reader. Inhibition and IC50 for each of the compounds were calculated with the XLFit curve fitting software (n=2, Z Factor, SW).





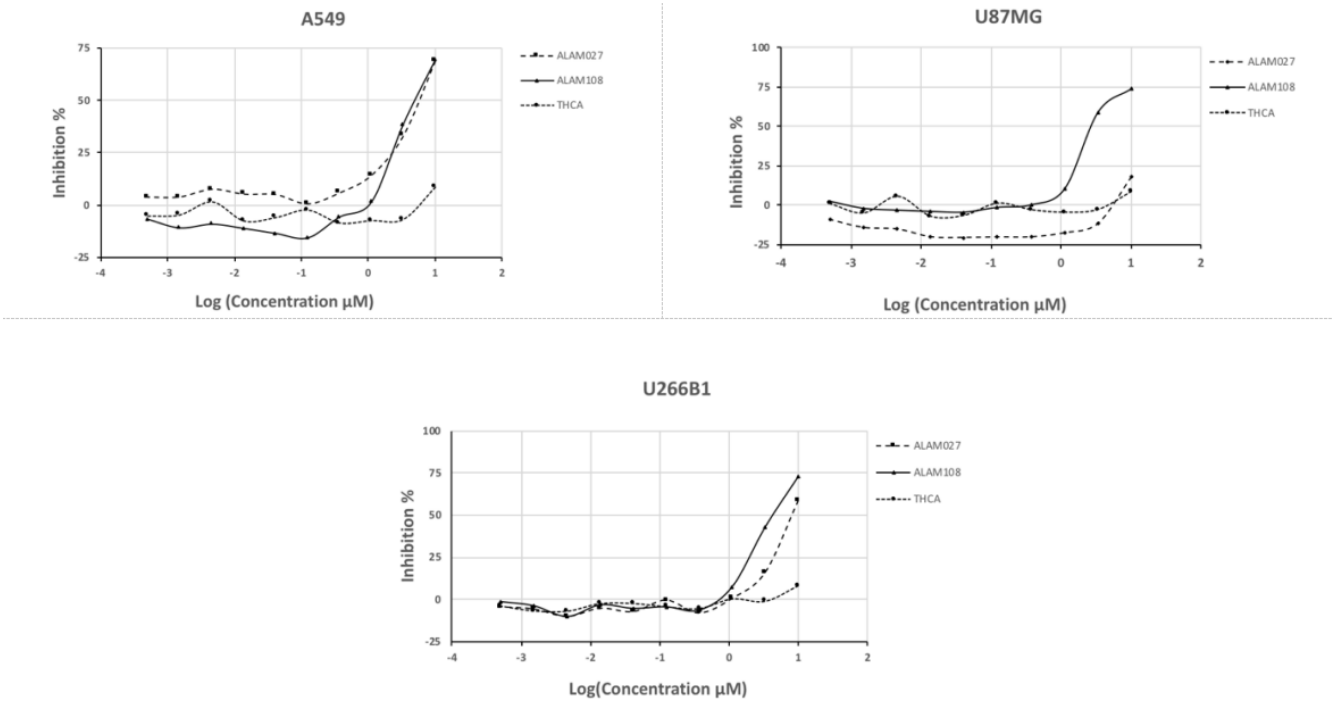


Figure 1. Growth inhibition curves of T47D, PC-3, HT-29, Caco-2, A549, U87MG and U266B1 cells at a wide range of THCA, ALAM027, and ALAM108 concentrations.

3.Results and Discussions

The structures of THCA and its derivatives ALAM 027 and ALAM108 are shown below.

The growth inhibition curves of T47D, PC-3, HT-29, Caco-2, A549, U47MG and U266B1 tumor cells as a function of THCA, ALAM027 and ALAM108 concentrations are shown in Figure 1.

Compared to its derivatives the level of THCA growth inhibition, was generally low for all cell lines examined but THCA did tend to inhibit T47D, A549 and U87MG cell proliferation to a greater extent than the other lines (Table 1).

For the T47D cell line, the ALAM027 compound shows good growth inhibition with an IC50 value comparable to THC (6.7 µM) and CBD (5 µM). The ALAM108 compound is less active, though its ability to inhibit cell proliferation significantly exceeds that of THCA.

The inhibition values of both cannabinoids on PC-3 prostate tumor cells are very similar (Table 1) but the ALAM027 compound yields a pleiotropic effect at 1 µM concentration following the growth inhibition.The comparison of both cannabinoid activities in HT-29 cells shows that these cells are more sensitive to ALAM108 than to ALAM027 while IC50 values of both compounds are much higher than those of CBD (23-30 µM) and THC (30 µM). However, in the case of Caco- 2 cells the IC50 values differ slightly and are comparable to those obtained in PC-3 cells.

The effect of ALAM027 and ALAM108 on A549 cells is practically the same both in terms of the degree of inhibition and IC50. When compared to THC (27.2 µM) and CBD (37.1µM)

[19] this advantage becomes clearly evident.

Regarding the U87MG cell line, compound ALAM027 shows a low-level activity comparable to THCA. Cannabinoid ALAM108 effectively inhibits cell survival with an IC50 of 3.37 μM that is on par with the activity of THC (IC50 1.2-14 μM) and CBD (IC50 1.5-9.7 μM) in this cell line. One of the possible reasons may be the ability of ALAM108 to pass through the blood-brain barrier due to its greater hydrophobicity (LogP 5.81) compared to ALAM027 (LogP 4.38). Perhaps this assumption is very relative, but currently available cannabinoid anticancer activity data on U87MG cells only relates to THC, CBD and some synthetic cannabinoids like WIN55,212-2.

The comparison of both cannabinoid activity against U266B1 cells shows the advantage of ALAM108 as for other cell lines.

Table 1. IC50 and inhibition values (10 μM) of THCA and its derivatives on T47D, A549, PC-3, HT-29, Caco-2, U87 MG, and U266B1 tumor cells.

Cancer cell lines	THCA		ALAM027		ALAM108		Parameters of screening assay*	
	Inhibition%	IC_{50} μM	Inhibition%	IC_{50} μM	Inhibition%	IC_{50} μM	Z Factor	SW
T47D	18.20	>10	97.90	5.52	47.20	>10	0.86	20.42
U87MG	10.52	>10	19.84	>10	73.80	3.37	0.93	45.37
A549	9.30	>10	77.08	5.59	70.01	5.53	0.83	17.22
PC-3	15.43	>10	61.13	9.94	63.61	7.45	0.81	12.68
HT-29	16.77	>10	86.21	6.27	88.13	1.99	0.85	18.99
Caco-2	12.99	>10	60.81	8.87	67.16	6.56	0.80	13.02
U266B1	8.68	>10	58.33	8.20	73.05	4.52	0.88	25.03

* [25]

4.Conclusions

Our current in vitro study of THCA derivatives ALAM027 and ALAM108 showed their antitumor activity in all the tumor cell types examined. The difference in the activity of these compounds in relation to the T47D and U87MG tumor cells may be indicative of different functional mechanisms.

Acknowledgment

The author thanks the employees of the Shanghai Chempartner (China) for their high professionalism and attention to his work.

Author Disclosure Statement

The author has no conflicts of interest, and no competing financial interests exist.

Funding Information

This work was funded from the AL&AM Pharmachem Ltd. company's own funds. (Grant ALAM2019-001).

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Spectrum of Pediatric Malignancies: An Observational Single Center Study from Western India

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ABSTRACT

Cancer is a leading cause of death for children and adolescent worldwide. The cure rates in low middle-income countries are dismal (20%) in comparison to high income countries (80%). The first move is to assemble precise data on epidemiology of pediatric cancer across the country and its region wide variation. This study attempts to provide spectrum of pediatric malignancies from a tertiary care hospital in the state of Rajasthan, India.

A total of 140 cases were studied retrospectively over a period of two years (April 2018-March 2020). Patients, 0-18 years of age that are diagnosed as a case of malignancy were included in this study. The records of these patients were retrieved and analyzed.

Patients were stratified in 4 groups; 0-4 years, 5-9 years, 10-14 years and 15-18 years. Most of the patients fell in 15-18 year group (35.7%), followed by 5-9 year group (28.5%). Majority of cases, 67.8% were male. The male to female ratio is 2.1:1. Leukemia (40%) was the most common malignancy followed by lymphoma, retinoblastoma and malignant bone tumors. Acute lymphoblastic leukemia comprises majority (35/56) of leukemia. Retinoblastoma was predominant malignancy among <5-year children. In all other groups, leukemia was predominant.

This study gauges the trend of pediatric malignancies at one of the largest tertiary care hospitals in Rajasthan, which is important in the planning and evaluation of health strategies. As we lack a dedicated pediatric cancer registry, such epidemiological studies play a significant part for this small but distinguished group of patients.

Keywords: Pediatric cancer;Epidemiology;Leukemia;Tertiary health care

1.Introduction

Cancer is one of the leading causes of death for children and adolescents around the world and approximately 300,000 children aged 0 to 19 years old are diagnosed with cancer each year.

In comparison to world, India has a lower incidence of pediatric cancer. As per the report of International Incidence of childhood cancer volume-3 (IICR-3), age-standardized rate of childhood cancer (0-19 year) incidence in India is 87.3 per million (pm) which is significantly lower than countries like US (180 pm), Canada (173.9 pm), Eu- rope (170-190 pm).

In India, data is collected through 33

population-based cancer registry and 29 hospital-based cancer registry which represents just 10% of population. This high-lights our knowledge gap regarding the true incidence of pediatric cancer in our country due to under reporting. Hence, leading to less diversion of resources for the management of pediatric cancer care and resulting in dismal outcomes in comparison to the western world. Moreover there is regional variation in reporting due to disparity in infrastructure and socioeconomic factors. Our study is an attempt to strengthen the pediatric cancer epidemiological data and emphasize the demographic variations.

2.Material and Methods

It is a retrospective observational cohort study conduct- ed over a period of two years (April 2018 to March 2020) in the department of medical oncology at a government tertiary health care cancer facility of Rajasthan after obtaining permission from concerned authority. The data of total 140 cases were collected from hospital records. All children aged 0-18 years, diagnosed as a case of malignancy by means of peripheral blood smears and bone marrow studies, cytological and histopathological examination during this period, were included in the study. Histological diagnosis was confirmed by our pathologist in all cases except for surgically inaccessible intracranial tumors. The records of these patients were retrieved and analyzed, focusing on the prevalence according to age, sex and types of tumors. For classification of pediatric malignancies in the present study, the International Classification of Childhood Cancers (ICCC), based on International Classification of Diseases for Oncology (ICD-O-3), was followed.

Statistical analysis

The data were entered in an EXCEL sheet and then analyzed. Descriptive statistics for continuous variables and frequency distribution, with their percentages were calculated as required.

3.Results

The data were recorded for 140 patients from age 0-18 years. Patients were stratified in four groups i.e 0-4 year, 5-9 year, 10-14 year and 15-18 year (Figure 1). Most of the patients (35.7 %) were placed in 15-18 year group (50/140), followed by 28.5% (40/140) patients in 5-9 year group. There were 18.5% and 17.1 % patients from age group 10-14 years (26/140) and 0-4 years (24/140). The mean and median age is 10.3 years and 11 years respectively in the present study. Sex wise distribution: Majority of cases, 67.8% were male (95/140) in comparison to 32.1% (45/140) were female (Figure 2). The male to female ratio is 2.1 in the current study.

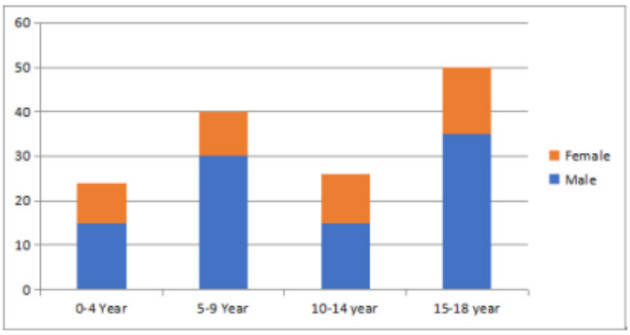

Figure 1. Stratification of patients as per age groups.

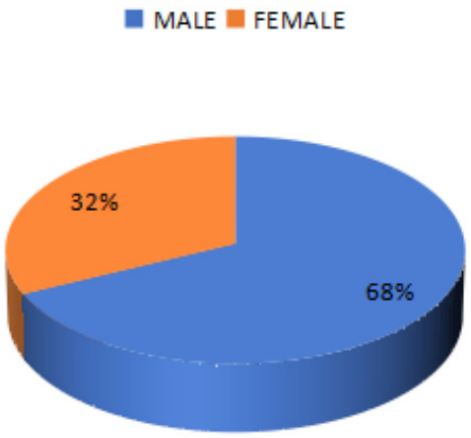

Figure 2. Sex wise distribution

Clinical Profile

Among all pediatric cancers, the most common was leukemia with 40% (56/140) of children affected (Figure 3/Table 1). The second most common was lymphoma 14.2% (20/140), followed by retinoblastoma 11.4% (16/140) and malignant bone tumors 10% (14/140). Germ cell tumor, neuroblastoma and renal tumors each constitute five percent (6/140) cases. Soft tissue sarcoma and CNS neoplasm were 5% (7/140) and 1.4% (2/140) respectively. Among others, there was a case of adrenocortical tumor in a 17-year-old boy.

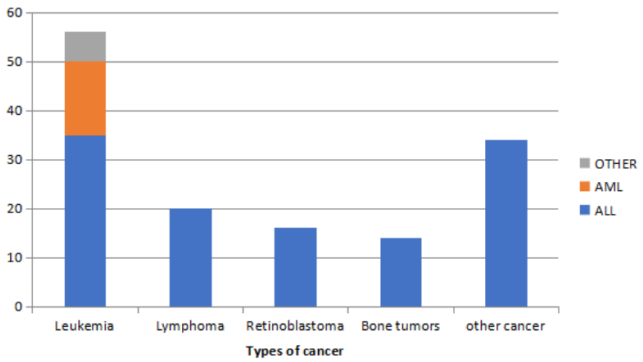

Figure 3. Frequency of various cancers among study population

Table 1. Distribution of various cancers along the age groups

S.no.	Type of cancer		0-4 Years	5-9 years	10-14 years	15-18 years	Total	Total (percentage %)
1.	LEUKEMIA	ALL	0	12	7	16	35	56 (40%)
		AML	1	3	3	8	12	
		CML	0	0	1	3	04	
		MDS	0	0	1	0	01	
		Unspecified	0	0	1	0	01	
2.	LYMPHOMA	Hodgkin lymphoma	0	3	1	6	10	20 (14.2%)
		NHL	2	2	0	2	06	
		OTHER	1	1	2	0	04	
3	CNS NEOPLASMS		1	0	1	0	02	2(1.4%)
4	NEUROBLASTOMA		1	3	0	2	06	6 (4.2%)
5	RETINOBLASTOMA		9	5	1	1	16	16 (11.4%)
6	RENAL TUMORS (Wilms tumor)		3	3	0	0	06	6 (4.2%)
7	HEPATIC TUMORS		0	0	0	0	00	0
8	BONE TUMORS	Osteosarcoma	0	0	1	2	03	14 (10%)
		Ewing sarcoma	1	2	4	3	10	
		Other	0	0	0	1	01	
9	SOFT TISSUE SARCOMA	Rhabdomyosarcoma	1	1	0	1	03	7(5%)
		Other STS	1	2	1	0	04	
10	GERM CELL TUMOR		2	1	0	3	06	6(4.2%)
11	CARCINOMA AND MELANOMA		1	0	0	1	02	2 (1.4%)
12	OTHERS AND UNSPECIFIED		0	2	2	1	05	5 (3.5%)
Total			24	40	26	50	140	140
Percentage			17.1%	28.5%	18.5%	35.7%		100%

Among the subgroup of leukemia, acute lymphoblastic leukemia was the most common with 62.5% (35/56) cases. The most common age group affected was between 15 to 18 years with male predominance. Acute myeloid leukemia was 10.7% (15/140) of all the cases. There were 4 cases of chronic myeloid leukemia, 3 of them lie in age group 15 to 18. There was 10-year-old boy having myelodysplastic syndrome. Among the lymphoma subgroup, Hodgkin lymphoma was the commonest with 7.1% (10/140) cases. There was again male predominance with only single female case out of 10. The most common age group affected was 15 to 18 years. There were 4.2% of non-Hodgkin lymphoma and 4 cases of unspecified lymphoma. Ewings sarcoma (7.1%) was the commonest bone tumor followed by osteosarcoma (2.1%). Most of our patients (80%) were started on treatment protocol as per the diagnosis (Figure 4). Seven percent refused for further treatment and 13% were referred to palliative or best supportive care.

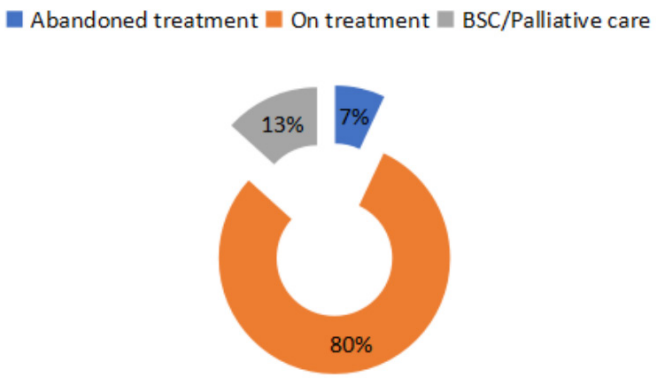

Figure 4. Follow up of the study cohort

4.Discussion

Childhood cancers are often neglected as they represent a small proportion of all cancers (0.7-4.4%). On the other hand when it occurs, it requires medical, psychological and societal concern. Childhood cancer incidence appears to be increasing in India. As we contain the morbidity and mortality caused by infection and malnutrition, childhood cancer attain increasing priority in our country.

In the report of International Incidence of childhood cancer volume-3 (IICR-3), age-standardized rate of child- hood cancer (0-19 year) incidence in India is 87.3 pm which is quite lower than countries like US (180 pm), Canada (173.9 pm) or Europe (170-190 pm). This discrepancy can be explained by delay in diagnosis, under-reporting, poor health care access, centralization of resources, less than 10% population coverage by cancer registries. 'Missing' cases can be attributed to myriad of reasons ranging from societal to availability of health care service.

In this study, we retrospectively analyzed the data regarding demographics and spectrum of malignancies in 140 pediatric patients (0-18 years) in a span of two years attending our tertiary health care facility.

As per IICR-3, ASRs were higher in children aged 0-4 years (ASR 197.1 pm) and 15-19 years (ASR 185.3 pm) than in those aged 5-9 years and 10-14 years. Similar observation made in our study for the age group 15-18 years of age (35.7%; 50/140 cases), but not for 0-4 years. The possible explanation can be that this age group of 0-4 years is obtaining treatment at the pediatric centre of our institute.

Incidence rates are slightly higher in boys than in girls (incidence sex ratio 1•14 in the 0-19

years age-group) and varied with age, region, and diagnostic group. In IICR- 3, the highest sex ratio incidence was reported from India (1.56) compared to 1.12-1.15 in high income countries (3). In our study, males were affected in 65.7% (95/140), while females were affected in 34.3% (45/140)cases. M: F ratio was 2.1:1. Similarly, Jussawalla et al (1.7), Das et al

(2), Nandkumar et al (1.8), Chauhan et al (2.2) and Bryan et al (4) reported high sex ratios in their studies. Although according to Kusumakumary et al, male predominance is a salient feature of many childhood tumors. This high ratio cannot be explained solely biologically or genetically but a large number of sociocultural practices play in their part. Gender-based discrimination is seen in Southeast Asian countries which results into delayed healthcare seeking for all childhood illnesses including cancer.

Childhood cancers are more commonly derived from hematopoietic system, central nervous system, soft tissue, bone and kidney in contrast to adults in whom skin, lung, breast, prostate and colon are the mostly affected. The three most common tumor in our study were leukemia (56/140; 40%), lymphoma (20/140;14.2%) and retinoblas- toma (16/140;11.4%). Bhalodia et al.,Pattnaik et al., Jan M et al., Chauhan et al and Chaudhuri et al. also reported leukemia as the most common pediatric malignancy in their studies. IICR-3 also reports leukemia as the most common cancer for 0-14 year but lymphoma among 15-19 year. Lymphoma comprises 16% (8/50) of patient among 15-18 year in this study. Our data found retinoblastoma as the most common malignancy among 0-4 year (9/24; 37.5%). Similar findings were reported by Jabeen et al and Hazarika et al. Leukemia was the most common malignancy among all other age groups (37-54%).

Malignant bone tumors were present in 10% (14/140) of our patients. This is in concordance with Pattnaik et al, Chauhan et al. [12] and Devi S et al. As in IICR- 3, renal tumors were common in children aged 0-4 years (3/24;12%) and 5-9 year (3/40;7.5%) and frequency decreased in older age groups (0%). ALL was the most commonly seen hematological malignancy (62%; 35/56 cases). This was in concordance with the studies of Bhalodia et al., Satyanarayana et al., Pattnaik et al. and Chauhan et al. Retinoblastoma was the most common non-hematological malignancy (16/64; 25%) followed by Ewing sarcoma (10/64; 15.6%). Chaudhuri et al. also reported retinoblastoma as the most common non-hematological malignancy (19.2%). There was no case of hepatic tumor in our cohort and CNS neoplasm was observed in only 1.4% (2/140) cases. This may be due to delay in diagnosis, poor availability of imaging techniques and their prohibitive cost.

A SIOP report stressed that refusal; non-compliance and abandonment of medical treatment remain critical issue. Although most of the patients (80%) in our study were started on disease-based protocol, further follow up data could not be retrieved. Twenty percent were not given disease specific treatment as few (7%; 10/140) refused and rest (13%; 19/140) had very advanced disease. Arora et al reiterates the problem of abandonment in the developing

countries for child hood cancer and suggests ways to improve treatment adherence.

Hence, we notice that various studies have shown in- consistent pattern of childhood cancer from our country. Retinoblastoma and leukemia were the most common malignancy in 0-4 year and 5-18-year group respectively. Leukemia, lymphoma, bone tumor and germ cell tumor occurred more commonly above five years of age, while retinoblastoma and Wilm's tumor were seen mostly in children less than five years.

Limitation

The present study is a single institution-based study. Small sample size and lack of follow-up served as a limitation.

5.Conclusions

This study gauges the trend of pediatric malignancies in Rajasthan, which is important in the planning and evaluation of health strategies. In India, where there is dearth of high-quality data as we lack a dedicated pediatric cancer registry, such epidemiological studies play a significant part for this small but distinguished group of patients.

Conflict of Interest

There was no conflict of interest.

All publication ethics were followed as per COPE guidelines.

Acknowledgement

I thank all my co-authors for helping, me to carry out this study and helping me to formulate the manuscript. I thank all the administrative and clinical staff in the department of medical oncology. At last, I extend my sincere gratitude towards all the patients and their families.

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Analysis of the Effect of Parathoracic Nerve Block and Compound Propofol Anesthesia on the Perioperative Period of Elderly Thoracotomy

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ABSTRACT

Objective: To explore the application of thoracic nerve block and propofol anesthesia in the treatment and perioperative period. Methods: A total of 40 patients with thoracotomy for esophageal cancer between May 2020 and September 2021 in the hospital were selected to participate in this study. All the patients were divided into reference and experimental groups according to the anesthesia protocol. For the experimental group, the parathoracic vertebral nerve block scheme was used under ultrasound guidance, with general anesthesia in the same manner, and after the surgical treatment of both groups, the patient-controlled intravenous analgesia (PCIA) regimen was applied to both patients. The time of surgery for the two patient groups, intraoperative propofol,postoperative pain conditions and postoperative blood glucose and NE, E, DA levels were measured and conducted for comparative analysis. Results: There is no significant differences between the two groups, besides, in the experimental group, propofol in surgery was less than that in the reference group; At the T6~T9 timepoint,patients in the experimental group had lower VAS scores in quiet and active conditions than those in the reference group; At the T9 timepoint, blood glucose and NE levels were higher than the T1,T4, T5 time point levels in each group; At the T4, T4 timepoint, Elevels in both groups were lower than the T1, T9 time point level in each group; at T9 time point, the DA level was higher in the reference group than the T1, T4 time point level in each group; at T9 Time point, blood glucose and NE, E, DA were lower than those in the reference group. Conclusions: In the treatment of thoracotomy in elderly patients, thoracic paravertebral nerve block compound propofol anesthesia program can be used to patients, with striking anesthesia effect and remarkable recovery effect in perioperative period, which is conducive to relieving postoperative pain and worth promotion and application.

Keywords: Thoracotomy;Parathoracic nerve block;Propofol

1.Introduction

In recent years, accelerated rehabilitation surgery has developed rapidly, and regional block has gradually become a key medical research field. In the treatment of surgical patients, simple general anesthesia scheme is generally applied to patients, and thoracic epidural block scheme can also be jointly applied to patients to achieve good analgesic effect. However, according to clinical

research, if epidural anesthesia is applied to patients, it will have a great impact on patient hemodynamics, and there are many operational risk factors, and some patients have a high incidence of postoperative complications. In recent years, parathoracic nerve block has been gradually applied in surgical treatment, which will only have a block effect on the surgical side of the patient, and will not exert a great adverse impact on the patient's body. In recent years, visual anesthesia technology has been prominently improved, and parathoracic nerve block technology has been gradually promoted and applied [1]. In this regard, in this study, a total of 40 patients with thoracic surgery for esophageal cancer between May 2020 and September 2021 were selected to take part in this study, to deeply explore the application of parathoracic vertebral nerve block compound propofol anesthesia in the treatment of elderly thoracotomy and the impact on the perioperative period of patients.

2.Materials and Methods

2.1General Information

A total of 40 patients with thoracotomy for esophageal cancer between May 2020 and September 2021 in our hospital were chosen to participate in this study, with American Anesthesia Association (American society of anesthesiologists, ASA) grade I or grade II, between 62 and 82 years, and average (69.1 ± 9.3). All patients were conscious and had normal cardiopulmonary function and did not receive preoperative radiotherapy, chemotherapy or blood transfusion regimens. During the perioperative period, none of the patients were treated with hormonal drugs. According to the different anesthetic protocols, all patients were divided into a reference group and an experimental group, in which 20 patients in the reference group were applied a simple continuous patient-controlled intravenous analgesia protocol, while 20 patients in the experimental group were applied a continuous thoracic paravertebral nerve block combined with a continuous patient-controlled intravenous analgesia protocol.

2.2Methods

Atropine 0.5 mg was applied to patients in both groups prior to surgical treatment, and was administered by intramuscular injection; after entering the operating room, patients were closely monitored, including heart rate (HR), bispectral index (BIS) and pulse oxygen saturation (SpO2) etc. Venipuncture was performed into the patient's right jugular and a double-tailed central vein catheter injected to prepare for intraoperative rehydration and venous blood extraction.

For the experimental group, an ultrasound-guided parathoracic vertebral nerve block protocol was used. The patient was assisted to take the lateral position, select the midline 1.5 cm~2.0 cm space of the rib space in the open chest, use it as the puncture point, routine skin disinfection, and 1% lidocaine was applied to the puncture point. Color Doppler ultrasound diagnostic instrument is chosen. For the ultrasound probe, it can be placed in the transverse plane and the perimeter of the puncture site is checked. During the exploration, the perpendicularity between the probe and the spine is maintained vertical, and a hyperechoic

band, i.e., the mural pleura, is visible laterally, while the anechoic region is the lung. In addition, on exploration above the mural pleura, dark echogenic strips were seen, i.e., the patient's ribs, and the thoracic paravertebral nerve was in the area between the above three. After the para- vertebral space images were obtained by ultrasound exploration, the images were analyzed, and a 21G-long 100 mm contrast puncture needle was inserted from the side of the ultrasound probe, and the anesthesia needle was placed into the paravertebral space under the guidance of the ultrasound machine, and 15 mL of 0.5% ropivacaine was injected after no blood was drawn back, and then the catheter was placed and fixed with a patch to assist the patient to lie flat [2]. After 10min, the effect of the nerve block was checked, and after passing the examination, the patient could be induced by general anesthesia.

The general anesthesia was the same in both groups, with mask oxygen inhalation and midazolam 0.05 mg/ kg~0.10 mg/kg, propofol 1.0 mg/kg~1.5 mg/kg, rocuronium bromide 0.6 mg/kg and fentanyl 4 mg/kg~6 mg/kg, by intravenous injection. The left two-cavity bronchial catheter is inserted and the ventilator is adjusted to intermittent positive pressure ventilation (IPPV) mode, the tidal volume can be controlled between 8 mL/kg~10 mL/kg, frequency 12 / min~14 / min aspiration ratio 1:2 and 35 mmHg~40 mmHg. In order to maintain the general anesthesia effect, propofol and remifentanil should be applied to patients by continuous intravenous infusion. Apart from that, rocuronium bromide is applied to patients and intermittent intravenous injection to maintain a good muscle relaxation effect. During the procedure, the patient blood pressure level and BIS value were closely monitored, and the anesthetic dosage was adjusted to control the patient blood pressure fluctuations within 20% of the preoperative monitoring value, while the patient BIS value was controlled between 50~60. In both groups of patients, 30 min before the surgical treatment, patients should also be applied dizocine 5 mg, tramadol 100 mg, toltestrone 6 mg.

After the completion of surgical treatment in both groups, intravenous patient-controlled analgesia (PCIA) protocol was applied to the patients. 2 μg/kg of sufentanil citrate, 10 mg/kg of tramadol and 8 mg of toltesetron were selected and added to 0.9% sodium chloride solution to prepare 100 mL of the mixture, and the continuous dose was set at 2 mL/h, 2 mL each time, and the locking time was set at 15 min. On top of that, for patients in the experimental group, an electronic pump formulation of 300 mL of 0.15% ropivacaine hydro- chloride at a continuous dose of 6 mL/h was applied.

2.3Observing Indicators

Time of surgery for the two patient groups, intraoperative propofol, postoperative pain conditions and postoperative blood glucose and NE, E, DA levels were measured and conducted for comparative analysis. The perioperative period varied from pre-anesthesia (T1), time (preinduction (T2), immediate tracheal intubation (T3), surgical 2h (T4), postoperative (T5), 1h (T6), 4h (T7), 8h (T 8), 24h (T9), 48h (T10). For the assessment of patients' pain, the pain visual analogue scale (VAS) was used, with a score out of 10, the higher the

score, the more intense the postoperative pain felt by the patient. At the detection of patient epinephrine (E), norepinephrine (NE), dopamine (DA) concentrations, after internal jugular vein sampling for 1h, plasma was collected by centrifugation at 2000 r/ min for 5 min, placed into a-70 ºC cryogenic refrigerator for storage and assayed by radioimmunoassay.

3.Results

3.1Comparison of Surgical Time and Intraoperative Medication between the Two Patient Groups

The time of surgery and the intraoperative medication statistics are shown in Table 1. The operation time difference between the two groups was not significant, and the amount of propofol in the experimental group was less than that of the reference group.

Table 1. Time of operation and intraoperative medication of the patients in the two groups

Group (n)	Time of surgery (h)	intraoperative propofol (mg)
Experimental Group (n=20)	4.0±0.6	960.0±216.8
Reference Group (n=20)	4.0±0.7	1242.5±200.1

3.2Comparison of Postoperative VAS Scores be- tween the Two Patient Groups

Postoperative VAS scores in both groups are shown in Table 2, at time points T6 to T9, the VAS scores of patients in the experimental group were lower than those of patients in the reference group when they were quiet as well as when they were active.

Table 2. Postoperative VAS scores and Ramsay sedation scores for the two patient groups (points)

Group (n)	Time point	VAS score in quiet	VAS score at activity
Experimental Group (n=20)	T6	0.5±0.1	1.6±1.0
	T7	0.6±0.2	1.2±1.0
	T8	0.7±0.1	2.0±0.7
	T9	0.7±0.1	2.0±0.8
	T10	1.5±0.6	2.9±0.7
Reference	T6	1.2±0.8	3.1±0.6
	T7	1.6±0.6	3.1±0.8
	T8	1.9±0.7	3.3±0.6
	T9	1.8±0.6	3.6±0.6
	T10	1.6±0.4	3.6±0.7

3.3Comparison of Postoperative Blood Glucose and NE, E, DA Levels between the Two Patient Groups

The postoperative blood glucose and NE, E, DA levels are shown in Table 3, where the blood glucose and NE levels were higher than the T1, T4, T5 time point, the T1, T9 time point, the T9 time point, and the T9 time point, the blood glucose and NE, E, DA in the experimental group were lower than the reference group.

4.Discussion

Thoracotomy will cause great trauma to patients, and it is easy to induce stress reactions. The incidence of postoperative adverse reactions is relatively high. Elderly patients have varying degrees of physiological decline and more perioperative complications. After thoracotomy, many patients experience cognitive dysfunction

Table 3. Postoperative blood glucose and NE, E, DA levels in the two groups

Group (n)	Time point	Blood glucose (nmol/L)	NE(ng/L)	E(ng/L)	DA(ng/L)
Experimental Group (n=20)	T1	5.4±0.4	196.6±55.6	176.6±55.6	36.7±15.6
	T4	5.7±0.8	155.0±26.4	85.0±26.4	72.0±23.4
	T5	5.3±1.1	142.5±25.0	62.4±35.0	19.4±29.9
	T9	7.4±1.2	321.0±43.0	170.1±69.0	57.5±34.0
Reference Group (n=20)	T1	5.6±0.6	189.7±48.6	175.6±54.1	39.8±18.6
	T4	5.7±1.1	149.0±26.2	69.0±24.4	862.2±18.1
	T5	6.3±1.1	139.4±22.0	52.4±24.0	62.5±18.9
	T9	8.9±1.1	467.0±40.0	207.1±71.0	92.2±33.1

and significant pain, and the effect of anesthesia has a greater impact on the patient's postoperative recovery. In recent years, the technique of regional block complex general anesthesia has developed rapidly and is more commonly used in thoracic surgical treatment. By comparing the thoracic paravertebral nerve block with the epidural tissue protocol, a good block of the torso on the operated side can be achieved without depressing the patient's heart.

In this study, for both groups of patients, for the experimental group, the ultrasound-guided thoracic paravertebral nerve block protocol was used, and the general anesthesia was the same for both groups, and the intravenous patient-controlled analgesia (PCIA) protocol was applied to the patients after the completion of surgical treatment in both groups. Time of surgery for the two patient groups, intraoperative propofol, postoperative pain conditions and postoperative blood glucose and NE, E, DA levels were measured and conducted for comparative analysis. When applying the thoracic collateral nerve block composite general anesthesia scheme to the patients in the experimental group, ultrasound technology was jointly used to ensure the location, direction and depth control effect of the puncture, and the operation success rate was relatively high [5].

According to the study, the experimental group patients' perioperative indicators are better than the reference group patients. It can be seen that in the treatment of thoracotomy in elderly patients, a thoracic paravertebral nerve block compounded with propofol anesthesia protocol can be applied to patients, which has significant anesthetic effect and the patient's perioperative recovery effect is significant and is conducive to the relief of postoperative pain, and is worth promoting and applying.

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Clinical Study of Endovascular Treatment of Severe Middle Cerebral Arter

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ABSTRACT

It is very important to study the factors affecting the incidence, progress and prognosis of patients with vascular dementia. 50 cases of severe middle cerebral artery stenosis or occlusion underwent endovascular treatment (25 cases of mild cognitive dysfunction, 25 cases of moderate cognitive dysfunction) were divided into two groups, where a medical drug treatment group and a control group established with 25 cases in each group. The cognitive function of each group of patients was evaluated before operation, 7 days after operation, 30 days after operation, and 180 days after operation. CTP was used to compare the hemodynamic changes in patients before and after operation. The severe stenosis or occlusion of the middle cerebral artery in patients can be improved, and the intracranial blood supply of patients with poorly compensated medial cranial circulation and hypoperfusion can be restored to a certain extent. Meanwhile, improvement of cognitive function was definitive in some patients with cognitive dysfunction. To guide the formulation of treatment plans for patients with severe middle cerebral artery stenosis or occlusion.
Keywords: Acute middle cerebral artery occlusion;Vascular cognitive impairment;Montreal cognitive assessment

1.Introduction

In recent years, vascular cognitive dysfunction has become the second most common cause of Alzheimer's disease in China, and the incidence is only lower than Alzheimer's disease. Non-dementia vascular cognitive dysfunction refers to early or mild cognitive impairment caused by cerebrovascular injury, and does not necessarily progress to vascular dementia; if it can be diagnosed and treated early in the VCIND stage, the course of the disease may reverse. Intracranial artery stenosis is closely related to the incidence of cognitive dysfunction, and endovascular treatment can better improve cerebral ischemia. The middle cerebral artery mainly supplies blood to the temporal lobe, parietal lobe and basal nucleus of the brain.

The more severe the stenosis of the middle cerebral artery segment, the higher the degree of cognitive impairment. Insufficient cerebral perfusion may be an important cause of cognitive impairment in patients with cerebral artery stenosis. The mechanism of cognitive dysfunction caused by cerebral hypoperfusion may include: long-term ischemia leading to chronic cerebral

ischemia, hypoxia, and anaerobic glycolysis, which induces phosphorous metabolism disorders in the brain hippocampal neuron membrane, producing excessive free radicals and releasing a large amount of excitatory amino acids, leading to intracellular calcium ion overload and other problems, resulting in hippocampus neurotransmitter disorder and neuron loss, causing cognitive impairment; white matterlesions are independent risk factors for cognitive dysfunction, long-term chronic ischemia and hypoxia can lead to diffuse demyelination changes in the white matter of the brain and accelerate cognitive decline; cerebral ischemia and hypoxia promote the production of β-amyloid, accelerate the aging and apoptosis of nerve cells, and lead to the decline of cognitive function. In addition, decreased cerebrovascular reserve capacity is also related to declined cognitive function. The pathogenesis of VCI is more complicated and the incidence is high. The incidence of VCI is increasing year by year, and the cost of treatment is relatively high. However, it is currently the only cognitive impairment disease that can be intervened. Recanalization of blood vessels may restore blood supply to brain tissue, and patients with severe stenosis or occlusion of the middle cerebral artery with cognitive impairment may benefit from it.

2.Materials and Methods

2.1Materials

50 patients with severe stenosis or occlusion of the middle cerebral artery (25 cases with mild cognitive impairment, 25 cases with moderate cognitive impairment) and 50 patients who received internal medications, hospitalized in provincial Grade III Level A hospitals from January 2019 to April 2020 were selected.

2.2Methods

From January 2019 to April 2020, 25 patients with mild to moderate cognitive impairment with severe stenosis or occlusion of one middle cerebral artery were included. The group receiving endovascular treatment was assigned as treatment group and the group receiving non-endovascular treatment was assigned as control group. CTP inspection was conducted. Inclusion criteria: Diagnosed with mild to moderate cognitive dysfunction by Montreal Cognitive Assessment (MOCA) screening (MOCA score<26 points); DSA showed severe unilateral middle cerebral artery stenosis or occlusion; Indications for end ovascular treatment. Exclusion criteria: Have a history of dementia and psychiatric diseases;

Severe middle

cerebral artery stenosis or occlusion causes blood supply area infarction; Severe systemic diseases or neurological deficits such as severe aphasia, unable to cooperate with cognitive function examination; History of alcohol, drug abuse, and psychotic drug abuse.

2.3 Examination Methods and Standards

With the subject's consent and cooperation, the Montreal Cognitive Assessment (MoCA) was used to evaluate and diagnose the subject's cognitive function. The assessment was arranged to take place in a quiet room whenever possible, and an experienced and professionally trained neurorehabilitation physician was appointed to conduct the assessment and record the assessment score. MOCA was conducted 1

week before operation, 7 days after operation, 3 months and 6 months after operation on the treatment group and control group during the same period. The MOCA scoring of cognitive function was evaluated by senior neurologists. The total score of MOCA score is 30 points. If the score is less than 26, it is considered that there is cognitive dysfunction. If number of years of education is less than 12 years, 1 point is added to the original score. Meanwhile, ReHo analysis was applied to the preprocessed resting state functional magnetic resonance imaging (MRI) data, and the data analysis was performed with the brain function data processing software developed by Beijing Normal University. Calculation was performed until each voxel of the whole brain reached consistency in time series with its 26 neighboring voxels in the surrounding. In the CTP examination, a CT scanner was used to determine cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and peak time (TTP), and then the CBF ratio (rCBF) of the affected side to the healthy side, CBV ratio (rCBV), MTT difference (dMTT) and TTP difference (dTTP) were calculated respectively.

2.4 Statistical Analysis

SPSS statistical analysis software was used. The measurement data are expressed as x±s. The independent sample t-test was used for comparison between the treatment group and the control group, and P<0.05 was considered as statistically significant.

3.Results

（1）Comparison of Treatment Efficacy

Table 1. Comparison of Treatment Efficacy

Group	90dmRS Score [Cases (%)]		mTICI Grading [Cases (%)]		Reocclusion Rate [Cases (%)]
	≤2 pts	>2 pts	≥2b	<2b	
Treatment (n=20)	13(65.00)	7(35.00)	17(85.00)	3(15.00)	2(10.00)
Control (n=20)	9(45.00)	11(55.00)	1	/	/
zX2	-1.	704			
P	0.	88			

（2）MOCA Score Comparison

Table 2. Comparison of each Item in MOCA Scoring

Item	Treatment Group	Control Group	P
Visual Spatial and Execution	2.8±1.0	4.7±0.5	0.00
Naming	2.6±0.5	2.9±0.3	0.14
Concentration	5.1±0.9	5.7±0.5	0.07
Language	2.1±0.7	2.9±0.3	0.01
Abstraction	1.8±0.4	1.8±0.4	1
Delayed Recall	2.9±1.0	4.2±0.6	0.00
Direction	4.8±0.6	5.2±0.8	0.23
MOCA	22.1±2.6	27.4±1.3	0.00

（3）Comparison of Difference in CTP between Groups

Table 3. Comparison of the CTP in the Mild Stenosis Group

	Affected Side	Healthy Side	P
CBV(m1/100g)	1.33±0.56	2.20±0.97	0.002
CBF(ml/100g/min)	20.17±7.94	30.67±13.39	0.023
TTP(s)	15.68±3.61	14.81±3.76	0.263
MTT(s)	3.58±0.78	3.52±1.04	0.842

Table 4. The Comparison of CTP in the Moderate Steno- sis Group

	Affected Side	Healthy Side	P
CBV(m1/100g)	1.17±0.68	1.85±1.15	0.011
CBF(ml/100g/min)	16.57±9.13	24.06±14.62	0.054
TTP(s)	16.55±5.81	12.54±2.46	0.003
MTT(s)	3.81±0.84	2.89±0.51	0.005

Value between Groups

Table 5. Regions with Significant Drop in ReHo Value in the Treatment Group

Brain Region	BA Area	Talairach Coordinate			t	Volume (mm)
		X	Y	z		
-Left Central Frontal Gyrus	6	-53	-12	64	-12.87	54
Left Frontal Gyrus	10	-15	55	12	-15.77	46
Lingual Gyrus of Right Occipital Lobe	17	12	-89	-3	-13.23	28
Lingual Gyrus of Left Occipital Lobe	17	-9	-89	0	-13.33	30
Left Middle Temporal Gyrus	21	-54	1	-19	-9.40	18
Left Precuneus	39	33	-65	36	-22.64	28
Left Posterior Cerebellum	-	-27	-69	-21	-34.06	48
Right Anterior Cerebellum	-	28	-37	-36	-11.46	31
Right Posterior Cerebellum	-	28	-80	42	-13.70	28

Table 6. Regions with Significant Drop in ReHo Value in the Control Group ReHo

Brain Region	BA Area	Talairach Coordinate			t	Volume (mm)
		X	Y	Z		
Left Medial Frontal Gyrus	6	-6	-9	61	9.93	36
Right Superior Temporal Gyrus	22	51	-18	0	27.75	33
Right Superior Temporal Gyrus	38	45	16	-27	21.29	29
Left Hippocampus	-	-19	-14	-24	18.89	38

4.Discussions

At this stage, patients with severe middle cerebral artery stenosis or occlusion have mainly three treatment options: endovascular treatment, surgical treatment and medical drug treatment. In recent years, with the development of endovascular treatment technology, continuous improvement of interventional devices and improvement of operational proficiency, the status of endovascular treatment in the middle cerebral artery is being valued by more and more scholars. However, there are not many studies on the intravascular treatment of the middle cerebral artery. The follow-up time is short, so the patients' long- term patency is not clear, and the long-term follow-up of hemodynamics is insufficient, especially the cognitive dysfunction is rarely assessed in some patients. Experimental and clinical studies have shown that for mild to moderate middle cerebral artery stenosis, the use of drug therapy and stenting can improve cognitive function; for severe middle cerebral artery stenosis or even occlusion,drug treatment cannot improve the cognitive function.

However, interventional therapy can significantly improve intracranial blood supply, thereby improving human cognitive function. After patients with severe middle cerebral artery stenosis or occlusion underwent endovascular treatment, their executive and memory ability may be significantly improved .

Vascular cognitive impairment refers to cognitive impairment syndrome, which ranges from mild cognitive impairment to dementia caused by cerebrovascular incidents. In many studies, the detection sensitivity of MOCA for mild vascular cognitive impairment is much higher than that of MMSE, which helps in the early diagnosis of vascular cognitive impairment and prevent vascular dementia in time. Therefore, in this study, we used the Montreal Cognitive Assessment Scale to assess the cognitive function of the subjects. The Montreal Assessment Scale showed that there were significant differences in visual

spatial, executive function, language and delayed recall between the treatment group and the control group, but the two groups had no significant difference in naming, concentration, abstraction and direction. In this study, central arteriovenous occlusion was assigned as the treatment group and endovascular treatment was performed. The blood flow of the middle cerebral artery was improved, but the patients' left-side visual spatial, executive, language and memory dysfunction, and concentration were not significantly different from those of the control group. Therefore, in this study, we found that patients with acute central arteriovenous occlusion have been successfully treated and recovered. Although they still have cognitive impairment, their concentration has been improved.

Current research shows that cerebral hemodynamic diseases caused by cerebral artery stenosis can be divided into four stages; stage 0 means that cerebral hemodynamics is completely normal; stage 1 means that as the cerebral perfusion pressure decreases, the body performs differently in level of actions. Cerebrovascular self-regulation dilates cerebral arterioles to reduce vascular resistance, and then reduce the ability of normal CBF by maintaining brain tissue, but at the expense of cerebrovascular reserve and CVR; the second stage is the further reduction of cerebral perfusion pressure. The cerebrovascular bed has reached the maximum expansion state, but the self-regulation ability of the cerebrovascular still cannot maintain the normal CBF of the brain tissue, and it is accompanied by the reduction in CBF and CVR failure. However, at this stage, the normal metabolism of brain tissue can be maintained by increasing oxygen intake. In the third stage, the oxygen uptake could not be maintained, but the decreased cerebral blood flow showed that it could not meet the continuous decrease of cerebral perfusion pressure of normal brain tissue.Cognitive function is a complex high-level brain function activity, accomplished not through a single brain area or neural structure but through multiple brain functional areas and neural structures. Studies have shown that memory functions involve many cortex and cortical structures. When brain damage occurs, the frontal lobe, temporal lobe, hippocampus, target gyrus, thalamus and midbrain reticular structure may further reduce. An- other study showed that the visual spatial function is accomplished by the frontal, temporal, parietal and occipital lobes, thalamus, basal ganglia and cerebellum in the two cerebral hemispheres. The results of this study show that middle cerebral artery infarction can impair visual spatial, executive, language and memory functions, and it supports cortical and subcortical structures to participate in related cognitive activities through specific neural net- works or circuits formed. Cerebral artery infarction can cause cognitive impairment in multiple areas.

Secondly, there is little difference in the good prognosis of neurological function between the two groups in this study, which may be affected by the sample size. Due to the relatively small sample size, the difference is unclear, but it can be seen that the endovascular treatment group has a higher good prognosis than the non-vascular treatment group. The study found that the speech score of the treatment group was

lower compared with the control group, which indicates that patients receiving endovascular treatment and those who have recovered from acute middle cerebral artery occlusion still have language disorders.

5.Conclusions

There is no obvious breakthrough in the treatment of acute middle cerebral artery occlusion and ischemic stroke, and the clinical prognosis of patients after medication is often not ideal. Therefore, in the real world, many neurologists perform endovascular treatment on these patients according to the guidelines, and the results are mixed. Among them, patients with middle cerebral artery occlusion recovered well after endovascular treatment, but their cognitive function was significantly lower than that of the control group. The two groups had significant differences in visual space, executive function, language and delayed recall, but no significant differences in naming, concentration, and direction. Compared with previous studies, the concentration of patients with acute middle cerebral artery occlusion who were successfully treated and recovered has improved. The functional strength of patients with middle cerebral artery occlusion after end- ovascular treatment is different from that of the control group.

Funding

Clinical Study of Endovascular Treatment of Severe Middle Cerebral Artery Stenosis or Occlusion and Vascular Cognitive Impairment.

Project No.: 2019zc184

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Progesterone Receptor Antagonists – A Novel Treatment for Severe Hyponatremia from the Endocrine Paraneoplastic Syndrome

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ABSTRACT

Hyponatremia related to ectopic secretion of cancer cells of arginine vasopressin (AVP) or atrial natriuretic peptide (ANP) is most commonly caused by small cell lung cancer. The ideal treatment would be one that not only corrects the hyponatremia, especially if it is life threatening, but at the same time causes regression of the cancer, and thus improves both quality and length of life. As one is waiting for chemotherapy, surgery, or radiotherapy to decrease the cancer burden, tolvaptan has been used to correct the hyponatremia to improve symptoms or prevent death. Mifepristone, a progesterone receptor modulator/antagonist has been used to treat various cancers. The oral 200mg tablet was given to an 80-year-old woman who developed sudden extensive lung cancer with a serum sodium of 118 mmol/L. She refused chemotherapy but agreed to take mifepristone. The hyponatremia was completely corrected (145 mmol/L) within one month of treatment. She was in complete remission for 5 years and died not from lung cancer, but an acute myocardial infarction. Mifepristone may serve the purpose to not only quickly correct hyponatremia when it is related to an endocrine paraneoplastic syndrome, but also to provide improved quality and length of life.
Keywords: Arginine vasopressor (AVN); Atrial natriuretic peptide (ANP); Lung cancer; Syndrome of inappropriate anti-diuretic hormone (SIADH);Mifepristone;

1.Introduction

Lung cancer is one of the most common cancers to cause endocrine paraneoplastic syndromes. When paraneoplastic syndrome occurs, the associated metabolic or endocrine disorder is related to the malignant tumor secreting hormones or peptides. One of these paraneoplastic syndromes is hyponatremia related to inappropriate secretion of the anti-diuretic hormone (ADH), and thus the condition is called the syndrome of inappropriate anti-diuretic hormone (SIADH).

The most common type of lung cancer associated with SIADH is small-cell lung cancer (SCLC) representing about 70% of the lung cancer cases (1). SIADH may be present in 7-16% of patients with SCLC. Though non-SCLC (NSCLC) has also been associated with SIADH, it only accounts for 1% of the cases

of SIADH resulting from a paraneoplastic syndrome .

Another paraneoplastic etiology for hyponatremia associated with lung cancer is the ectopic secretion of the atrial natriuretic peptide (ANP). Studies of SCLC cell lines have demonstrated that ectopic ADH, and ANP, are equally likely to be the cause of the hyponatremia, and not uncommonly both may be increased at the same time.

The prognosis for patients with lung cancer with hyponatremia is worse than those with normal serum sodium levels. Serum sodium levels <125 mEq/L are associated with an extremely poor prognosis, with death generally within two weeks associated with severe brain edema that is associated with very low sodium levels with the resulting low plasma hypo osmolarity leading to headache, memory impairment, generalized muscle weakness and associated fatigue, seizures, nausea, and psychiatric dysfunction progressing to coma and death.

Chemotherapy, possibly combined with surgery or radiotherapy, and supportive measures are the main treatment modality for hyponatremia associated with lung cancer. If one achieves a remission following chemotherapy, there is a high success rate in correcting the hyponatremia. However, with tumor recurrence, the hyponatremia generally also returns. In very rare circumstances, aggressive chemotherapy may be associated with marked hyponatremia related to sudden excessive release of stored ADH (otherwise known as arginine vasopressin AVP)) and ANP.

A case is reported of probable rapid onset very aggressive SCLC, with marked hyponatremia, who had quick resolution of the hyponatremia, not with chemotherapy, but with a progesterone modulator/antagonist.

2.Case Report

A 78-year-old woman was first diagnosed with chronic lymphocytic leukemia (CLL). Since she was asymptomatic, she was given no therapy but continued observation and evaluation by blood studies. With continued slow progression of leukocytosis (38,000) and mild thrombocytopenia, and with the development of some symptoms of dyspnea on exertion and weakness, her hematologist when she was age 80 decided to try treatment with oral chlorambucil.

Three days after starting the chlorambucil her clinical status significantly deteriorated with confusion, extreme weakness, and severe respiratory distress. Three months prior to her admission to the hospital for this acute decline in her health status, it was noted that she had mild hyponatremia of 130 mmol/L. On admission her serum sodium was life threatening at 118 mmol/L. By manipulating fluid intake and administration of electrolytes intravenously, her serum sodium increased to 122 mmol/L. Her serum PO2 on admission was 72 mmHg.

A chest x-ray revealed extensive pulmonary nodules with the radiologic diagnosis of metastatic lung cancer,or less likely, rapidly advancing lymphoma, as opposed to rapid progression of her CLL to a more acute leukemia process.

A biopsy of a pulmonary lesion with possible chemo- therapy was recommended, but

she refused this management. However, after a brief discussion, she agreed to be treated with oral mifepristone 200 mg/day as an outpatient. A compassionate use investigational drug approval (IND) was obtained from the United States Food and Drug Administration and her treatment was approved by the Western Institutional Review Board.

She clinically was much improved after two weeks of treatment. After one month of treatment her PO2 was 99- 100 mmHg without supplemental oxygen. Her serum sodium level was normal at 145 mmol/L.

After 2 months of treatment her computerized axial tomography (CT-scan) showed mostly complete resolution of all of her lung nodules with those remaining much smaller.

Subsequent chest x-rays over the next 5 years continued to demonstrate no pulmonary nodules just a ground glass appearance to the lungs. Her PO2 and serum sodium were continually normal. Her CLL did seem to respond to the very short course of chlorambucil and the CLL just slowly progressed over these 5-year period requiring no additional therapy.

At age 85 while sleeping she had an acute myocardial infarction, and she was pronounced dead when she arrived by rescue squad to the hospital's emergency room.

3.Discussion

The radiologists and oncologist based on chest x-ray and CT scan were convinced that the woman was suffering from lung cancer, but rapidly advancing lymphoma was a much less likely possibility. However, without a pathological diagnosis, they could not determine if the woman was suffering from SCLC or NSCLC. However, based on the very rapid aggressive onset, and the fact that hyponatremia related to excessive secretion of AVP or ANP is much more common in SCLC vs. NSCLC (or lymphoma), her oncologist favored SCLC as her diagnosis.

It is not clear if the severe sudden drop in serum sodium was related to rapid advancing lung cancer, or did the chlorambucil treatment, which was given for CLL (and would not be a very effective treatment for lung cancer), caused cell lysis with acute release of AVP or ANP further exacerbating preexisting SIADH from mild ectopic AVP or ANP release from lung cancer cells?

Mifepristone has been proven to be an effective treatment for advanced lung cancer providing significant improved quality and extension of life. Mifepristone has provided similar benefits in patients with a variety of different advanced cancers. The mechanism of action is thought to be secondary to its effect on blocking membrane progesterone receptors that are needed to make a protein called the progesterone induced blocking factor (PIBF) . This PIBF protein is unique with no amino acid homology to any known protein, is needed by both the fetal-placental unit and cancer cells to proliferate, invade, tissue and escape immune surveillance, but is not essential for everyday life in people that are healthy.

Tolvaptan has been used to treat cancer patients with hyponatremia due to SIADH. Tolvaptan is an oral selective V2-receptor antagonist. AVP normally acts on V2 receptors

in the renal collecting duct to promote free water absorption, thereby increasing extracellular fluid volume. The continued upregulated expression of AVP in paraneoplastic SIADH leads to excessive dilution of free sodium which leads to the state of hyponatremia.

In the post-hoc analysis of the SALT-1 and SALT-2 trials, 7 of 8 taking tolvaptan normalized their serum sodium vs. 2 of 16 placebo controls. A previous study found similar results. Tolvaptan could be used concomitantly with mifepristone to try to get the hyponatremia corrected in case the mifepristone is not able to cause regression of that particular patient's cancer. In that case, the tolvaptan could be used with the drug of choice for treating that cancer.

Nevertheless, the best treatment for the hyponatremia is to correct the cause of ectopic production by cancer cells of AVP or ANP, since the obvious goal is to prolong and improve quality of life. Nevertheless, tolvaptan seems to be a reasonable short-term solution in case the person could die from the hyponatremia before regression of the cancer is obtained by mifepristone, chemotherapy, radiotherapy or immune therapy. Nevertheless, in the case reported here, rapid correction of the severe life-threatening hyponatremia related to SIADH was solely related to mifepristone therapy.

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Research Progress on the Influence of Movement Instruction on Community Life in Patients with Coronary Heart Disease

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ABSTRACT

The incidence of coronary heart disease increases year by year with the material level of our country. It has a harmful effect on the patient's life health and quality of life. Movement Instruction is an important aspect of the secondary prevention project of cardiac rehabilitation in patients with coronary heart disease. Although it has a history of decades at inland and abroad, the present situation in China is not optimistic. Some studies have shown that the popularization and participation of cardiac rehabilitation is true and lacking. This paper sums up the relevant knowledge of coronary heart disease, coronary heart disease movement instruction and its impact on community life of patients at home and abroad, and reviews the research results of movement instruction on community rehabilitation of coronary heart disease in recent years, which provides a theoretical reference and prospect for the future research of community exercise rehabilitation of coronary heart disease.

Keywords: Coronary heart disease;Community rehabilitation;Quality of life

1.Introduction

With the development and progress of society, the improvement of people's living conditions has grown up to be a major cause of cardiovascular disease, and the incidence rate is increasing year by year. Coronary atherosclerotic heart disease (Coronary atherosclerotic Heart Disease, CHD) Coronary heart disease (CHD) is caused by ischemia or necrosis of the myocardium caused by imbalance of coronary blood supply and myocardial oxygen demand, which in turn leads to the occurrence of heart disease. Many years of research have confirmed that hypertension (hypertension. Hp) is the most dangerous neutral factor in the CHD of blood. Exercise rehabilitation is an important part of the secondary prevention program of heart rehabilitation in patients with coronary heart disease. Movement instruction is an important aspect of exercise rehabilitation, movement instruction can improve cardiopulmonary function according to the patient's history of disease. In our country, the popularity

and participation of cardiac rehabilitation are relatively scarce. The treatment of cardiovascular diseases is becoming more and more mature, but cardiac rehabilitation is limited to the third Class A hospitals. Movement instruction can be completed by rehabilitation therapists and rehabilitation physicians in the hospital, and exercise prescriptions are delivered by rehabilitation physicians. Patients are advised to train under the guidance of rehabilitation therapists, but most of the patients with coronary heart disease are located in various communities, where the lack of scientific movement instruction and appropriate training is not optimistic. Based on this, this paper reviews the research on the effect of exercise on the life of patients with coronary heart dis- ease in the community.

2.Research Progress on Coronary Heart Disease

2.1Incidence and Fatality Rate

Coronary heart disease is caused by various causes such as hyperlipidemia, hypertension, smoking, coronary obstruction and stenosis, which in turn lead to myocardial ischemia, angina pectoralis and even myocardial infarction. The incidence in our country is very high, the fatality rate also remains high all year round. In addition, coronary heart disease remains the leading cause of high mortality in developed countries and globally, except in developing countries such as China.

2.2Effects on Life

Some patients with coronary heart disease may develop symptoms such as poor sleep quality, loss of appetite and anxiety and depression along with increased psychological stress. Most patients with coronary heart disease in China are more inclined to receive relatively meticulous and high-level treatment in Grade 3A hospitals. In the long run, not only the patients' own economic burden will become heavier, but the medical social resources will also be wasted because of long-term occupation.

3.Research Progress of Movement Instruction for Coronary Heart Disease

A large number of studies have shown that proper exercise training in patients with coronary heart disease is helpful to establish coronary collateral circulation, improve blood supply of cardiac muscle cells, and improve cardiopulmonary function, Chen Jianjian et al graded motion tests. The patients with coronary heart disease were subjected to incremental load exercise, and the corresponding targeted aerobic exercise was tested to confirm that professional cardiopulmonary movement instruction could improve the cardiopulmonary function of the patients. Chen Xuanzu and others individualized movement instruction was used to guide patients with coronary heart disease cardiac function grade III and above to carry out a control test, adjust exercise intensity, exercise frequency, exercise type and exercise time according to different patient conditions, customize individualized exercise prescription, urge patients to train and follow up regularly. The control results confirmed that individualized movement instruction could improve blood glucose and blood lipids in patients with coronary heart disease. A meta-analysis showed that traditional Chinese medicine exercise

therapy such as Taijiquan and Baduanjin can effectively improve the physical function and mental state of patients. Yue Shuang et al with the concept of "double heart" treatment, the author emphasizes the improvement of heart function of patients with coronary heart disease and pays attention to its common psychological problems. Negative emotions such as anxiety and depression can increase the risk of coronary heart disease and death, Li Xinpeng and others. For patients with coronary heart disease with negative emotions such as anxiety and depression, traditional Chinese medicine rehabilitation exercise was used to guide exercise, improve the negative emotions of patients and improve the quality of life of patients. Movement instruction not only affects the above physiological and psychological factors in patients with coronary heart disease, but also a large number of evidence-based medicine. Evidence also suggests that cardiac rehabilitation movement instruction can effectively delay the development of coronary atherosclerosis. To prevent recurrence, repeated admission treatment, while relieving the economic pressure of patients while prolonging the survival time.

4.Study on the Influence of Exercise on Community Life of Patients with Coronary Heart Disease

4.1Research on Community Life of Coronary Heart Disease Patients Guided by Exercise in China

Guo Yuanhang, there are more than 500 specialized heart rehabilitation centers in China up to 17 years. Some areas such as southwest and northwest lack attention to cardiac rehabilitation. As an important part of heart rehabilitation, movement instruction requires professional guidance from rehabilitation therapists and rehabilitation physicians, while the number of rehabilitation teams in China is at present. Not enough to meet over 700,000 people per year. The needs of surgical patients. At present, the importance of cardiac rehabilitation in China is not high. The patients didn't realize the value of cardiac rehabilitation correctly, and the exercise prescription wasn't long-lasting. At the same time, Professor Lu Xiao said that in order to improve the safety factor. Emergency drugs should be prepared at the side of the training, and rehabilitation therapists should be required to master certain knowledge of first aid. If patients in the community for remote movement instruction should also follow in order to prevent accidents, timely rescue. Under the hierarchical medical system. Therapists in community hospitals will be responsible for the exercise of coronary heart disease in the community, rehabilitation outside the hospital, and effective conservation of medical resources. Timely professional assessment of patients within the community consolidation of curative effects. However, there is still a problem of uneven distribution of local medical resources, North and South China generally attach importance to the third phase rehabilitation of patients with coronary heart disease. Therefore, as mentioned above, movement instruction affects the physical and psychological factors of patients with coronary heart disease.

4.2Progress of Community Life Influence in

Coronary Heart Disease Patients

Report pointed out that the number of deaths due to cardiovascular diseases in China increased year by year in 2016, while the number of deaths due to cardiovascular diseases in foreign countries, such as Japan, the United States, Germany and other countries a year earlier. The European and American countries have formed a mature system, the community center and rehabilitation center docking, to ensure that patients in the community can receive regular rehabilitation therapists for their movement instruction, and more humane settings such as treatment groups, patients can communicate and interact. The system of pre-hospital and in-hospital heart rehabilitation is more mature, such as the closed-loop model in the United States, where rehabilitation teams work together to complete a set of movement instruction programs and supervise implementation. In Asia, Japan also has a more mature heart rehabilitation system because of its early integration with the European and American systems. It is also worth learning in the direction of long-term rehabilitation outside the hospital. Because the system is relatively mature, community exercise in these countries guides patients with coronary atherosclerotic heart disease to complete the training program issued by the rehabilitation team.

5.Conclusion

With the leap of the material level and the improvement of living conditions, the number of patients with coronary heart disease in China is increasing year by year, and the incidence, mortality and treatment are not optimistic. Coronary heart disease rehabilitation as an important post-operative recovery means for patients with coronary heart disease can effectively enhance the quality of life and improve the recovery effect. His role has been paid more and more attention by researchers at home and abroad. And related research is gradually increasing. However, the popularization of community rehabilitation still needs to be strengthened, the theoretical system of coronary heart disease rehabilitation is expected to be more and more perfect, and the primary therapeutic treatment for patients with coronary heart disease is more and more.

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Research Progress on Job Burnout of Family Doctors

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ABSTRACT

Job burnout is an important factor affecting the work attitude and professional behavior of family doctors. This paper reviews the measurement tools, influencing factors and intervention strategies of job burnout, it is suggested that improving job burnout can improve job satisfaction, work efficiency and reduce turnover intention of family doctors, and it is of great significance to the construction of family doctor team and the improvement of work quality.
Keywords: Family doctor;Influencing factors; Job burnout; Measuring tools; Intervention strategies

1.Introduction

Burnout, also known as "job burnout", refers to the state of physical and mental fatigue and energy exhaustion in the face of continuous workload[1]. The term "job burnout" was first put forward by American psychological expert Freudenberger and then summarized by Maslach.[2] The psychological syndrome caused by continuous emotions and interpersonal stressors at work is called job burnout. As an important support of community health management, family doctors undertake the management of chronic diseases, infectious diseases and population health management tasks, with heavy workload and heavy medical tasks. They are the potential high incidence group of job burnout. Job burnout will affect the family doctor in work.[3-4]

2.Job Burnout of Family Doctors

The research on family doctors' job burnout was carried out earlier abroad. The United States, the United Kingdom, Germany and other countries, which are the first European countries to implement the family doctor service model, have carried out relevant research and achieved a series of results.[5] According to a study on the job burnout of 27276 doctors carried out by US researchers, the incidence of job burnout of general practitioners in family medicine field is higher, ranking in the top five. [6] conducted a job burnout analysis of 232 family doctors in the UK from March 2016 to August 2017, and the results showed that 22.7% and 72.7% of general practitioners in the field of family medicine were in the top five the degree of job burnout is related to family doctors' job well-being. In Germany, researchers selected 214 general practitioners for analysis and found that female doctors had a higher risk of emotional exhaustion and a lower degree of job satisfaction.[7] A survey of 683 general practitioners in Ireland shows that age and gender are related to the degree of job burnout of family doctors.[8-9] conducted a cross-sectional survey of 196 general practitioners and found that the incidence of moderate and high emotional exhaustion, depersonalization and

personal accomplishment were 34.7%, 33.5% and 67.8% respectively. Researchers analyzed 183 general practitioners in Israeli community medical centers, and found that job burnout of general practitioners in the community was affected by job stress and job satisfaction.[10] In Japan, researchers found that the level of job burnout of middle-aged general practitioners is higher than that of young family doctors. [11] In contrast, the domestic research on family doctors' job burnout is less than that abroad. Researchers investigated the job burnout of 85 general practitioners working in Shanghai suburban community health service centers, and found that the incidence of moderate and severe job burn- out was 40.0%, and the job burnout was serious among the selected general practitioners; Others investigated 135 general practitioners nationwide, and the results showed that job burnout had an impact on their turnover intention People with high level of burnout are more willing to leave. Combined with the research and analysis at home and abroad, the degree of job burnout affects the work of family doctors, relates to the work efficiency and quality of staff, and becomes a key topic in the psychological aspect of community family doctors.

3.Influencing Factors of Family Doctors' Job Burnout

The influencing factors of family doctors' job burnout include many aspects, including individual, social, organizational and other factors. Job burnout brings pressure to family doctors, and a higher degree of burnout may even affect their physical and mental health.

3.1Individual Factors

Through research concluded that there is a positive correlation between age and the level of job burnout, and the level of job burnout of the elderly is higher than that of the young. [12] At the same time, the degree of job burnout is also affected by the individual's own personality traits. Compared with extroverts, introverts have higher degree of job burnout. Researchers conducted a survey on family doctors in Hungary, and found that the incidence of female job burnout is higher than that of male, which may be related to female family doctors' need to bear the dual pressure of occupation and family. Therefore, they are more likely to have job burnout than male family doctors.[13]

3.2Social Factors

The family doctor model originated in foreign countries and began to be carried out in China in 2012, which was gradually promoted by Shanghai, Beijing, Hangzhou and other cities. [14] The social factors influencing family doctors' job burnout are related to the local government's investment in community health care and the trust relationship between doctors and patients. Due to the difference between the development time of family doctors in China and the amount of funds invested by the government in the community health system, in cities with earlier development time and more developed economy, the government has invested more in the medical service of family doctors. The survey shows that the degree of job burnout of family doctors in cities with high economic level is higher than that in cities with low economic level. [15] The degree of harmony between the contract signing group and the

family doctor team members also has an impact on the job burnout of family doctors. During the follow-up, the medical staff with high degree of trust and cooperation with the contract signing crowd had better job burnout.[16]

3.3Organizational Factors

The organizational factors influencing family burnout include occupational stress, work environment, work family conflict, role influence and organizational sup- port.[17] Experts found that workload has a significant impact on job burnout. conducted a survey on primary health care workers in Malaysia.[18] The results showed that the satisfaction of the staff to their departments would affect the level of job burnout, and the staff with low satisfaction to their units and departments had a higher level of job burnout. Nantha found that the infrastructure of institutions is not perfect, and the working environment is poor, especially in some economically underdeveloped areas, which will make the grassroots medical staff lose their enthusiasm and vitality for work.[19] Experts conducted two surveys on primary care doctors in the United States, and the results showed that adverse working conditions would deepen the degree of job burnout and reduce job satisfaction.[20] At the same time, the conflict between work and family will also affect the level of job burnout, medical staff as a member of the family, for the family is very important. Research's found that after alleviating work family conflict, the level of job burnout decreased.[21] As the role of family doctor is the bridge between community medical service and contract signing population, family doctor needs to complete his own task and take responsibility due to his work responsibility and expectation. We should not only be responsible for the contract signing crowd, but also deal with the role that should be done to adapt to the work mode, so the degree of role adaptation has an impact on the job burnout of family doctors. Lack of support and encouragement in work will also affect the job burnout of family doctors. In the face of work, the job burnout of the staff with higher support from leaders and colleagues and harmonious relationship among colleagues is better.[22]

3.4Other Factors

The job burnout of family doctors is also affected by some other factors. For example, researchers found that the personal coping ability of family doctors has a significant impact on the job burnout of family doctors in medical work.[23] Others found that the relevant training needs and academic requirements of doctors are important influencing factors of job burnout.[24]

4.Intervention Measures and Coping Strategies of Family Doctors' Job Burnout

4.1Relieve Fatigue Based on Mindfulness Training Mode

Mindfulness training (MT) was proposed by Dr. karbakin of Massachusetts University in 1979 at Massachusetts Medical College. It is applied in the field of medical care to help staff alleviate negative burnout, reduce work anxiety, objectively evaluate and accept themselves, improve negative thinking and eliminate negative energy in their hearts.[25] The research of foreign experts shows that after four weeks of mindfulness training, the degree of job burnout of the participants has been alleviated, the

symptoms have been improved, and they have a higher love for themselves and their work. Domestic researchers found that the job burnout of the medical staff in the blood purification center has a significant improvement effect, reducing the effect of anxiety and job burnout, and improving the bad mood. Researchers shows that through mindfulness training for 4 weeks and 8 weeks, family doctors' job burnout is improved, and the training effect of 8 weeks is better, and their job satisfaction is higher. [26] The results show that mindfulness training can reduce the burnout of medical staff and improve their well-being. In addition, according to the study, mindfulness training can improve the quality of sleep, help the body maintain a peaceful state of mind, and then improve the status of job burnout.[27] Therefore, through this way, from the physical and mental point of view, reduce psychological negative energy, eliminate bad emotions, and reduce the degree of burnout.

4.2"Balint Group Sharing Communication Method" Was Used to Reduce Burnout

Balint group method, named after Balint, a famous psychoanalyst, was first applied to family doctors as a means of communication in their work practice, usually in the form of group discussion. In 2003, German research experts introduced Balint group method into China, and first applied it in the training of Shanghai Tongji Hospital, a general hospital. The selected research object was community family doctors at first, and then it was extended to other medical staff in the medical field, including nurses, medical managers, etc., and achieved good results. The results show that: through Balint group, community family doctors can better understand their own work, alleviate the job burnout of community family doctors, improve the professional skills of medical staff and improve the doctor-patient relationship. Through empathy and communication skills, we can better understand each other's professional identity and increase job satisfaction. Foreign studies also show that Balint group activities can help family doctors better deal with difficult clinical situations, improve communication skills, further promote the development of doctor-patient relationship, release work pressure and improve job burnout. Researchers used Balint method to randomly divide the family doctors into two groups.[28] The intervention content included two lectures and 10 Balint courses for six months. After the training, all participants measured and evaluated the job burnout and job satisfaction before and after the intervention. The results showed that Balint group interactive communication method could meet the needs of medical staff the level of job burnout was lower than that before the test. Researchers proved that this method can effectively reduce the burnout of family doctors by carrying out the Balint group method for at least one year and com- paring the job burnout before and after the training.[29] The research shows that the family doctors trained by Balint method have higher enthusiasm in work than those not trained by Balint method. Therefore, it is feasible to take Balint group method to alleviate the job burnout of family doctors. Balint group method can be further developed and spread to reduce the job burnout of family doctors.

5.Conclusion

To sum up, there are many researches on family doctors' job burnout at home and abroad, while there are few literatures on coping strategies and intervention of family doctors' job burnout. Therefore, further exploration and practice are needed to help family doctors establish a good working attitude, maintain a positive and enthusiastic working state, improve the team's collective quality, and promote the development of community medical practice.

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The Significance of Cytoskeleton System in Tumor Cell Infiltration

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ABSTRACT

Cytoskeleton system is mainly composed of three kinds of fibrils: microtubules, microfilaments and intermediate filaments. They are a complex network of protein filaments in the cytoplasm of eukaryotic cells. They not only act as scaffolds in cells, but also play an important role in maintaining the movement of cells, participating in the material transport and signal transmission in cells. It is found that the whole cytoskeleton system is closely related to tumor invasion and growth. Therefore, this article reviews the overview of the cytoskeleton system and its significance for tumor cell invasion and growth.

Keywords: Cytoskeleton system;Tumor cells;Infiltration

1.Overview of the Cytoskeleton System

The cytoskeleton system refers to the protein fiber net- work framework in eukaryotic cells. It is a three-part system consisting of microtubules (MT), microfilament (MF) and intermediate filaments (IF) composition. The three are highly coordinated and distributed, and are connected with the nucleus, cytoplasmic membrane, and organelles to form a cell morphology skeleton and movement coordination system to maintain the shape of the cell and maintain the function of cell movement, and have important significance for signal transmission. The cytoskeleton system, the genetic system within the cell, and the biofilm system are collectively called the “three intracellular systems”.

2.The Structure and Function of Microtubules and Tumor Cell Infiltration

Microtubules are hollow tubular structures with a diameter of 24-27 nm and an inner diameter of about 15 nm. They are distributed in the cytoplasm and nucleus of many cells. The tube wall is surrounded by 10-13.5 nm protofilaments. The tube length varies from a few microns to a few centimeters. Microtubules can be assembled into single tube, double tube and triple tube, which are found in structures such as cilia, centrioles and spindles, respectively. Microtubules have functions related to cell support, movement and cell division. In addition, it also participates in the transport of intracellular substances. Microtubules constitute the reticular scaffold of cells to maintain cell morphology; participate in

cell contraction and pseudopodia movement; participate in the displacement of organelles, especially the division and displacement of chromosomes, which require the help of microtubules. It may also participate in the transportation of substances in the cell, and may play a role in the microcirculation system of transporting macromolecular particles in the cell. The infiltration and metastasis of tumor cells is one of the biological characteristics of malignant tumors. The active mobility of tumor cells is an important factor in infiltration and growth. Microtubules, one of the components of the cytoskeleton system, are dispersed in the cytoplasm and move in normal cells. And it plays an important role in the activities of tumor invasion.

In traditional concepts, microtubules determine the shape of cells and play a role in mitosis and organelle transport. However, recent studies by Gomez et al. showed that although the structure of microtubules has an impact on cell morphology, changes in cell shape have a greater impact on the structure of microtubules. They used Drosophila embryonic cells as target cells, treated the cells as nearly elliptical, and used the cell aspect ratio, eccentricity, and microtubule standard deviation and microtubule deviation as indicators to compare cell shape changes and microtubule structure changes. They first knocked out the embryonic cell's blastocyst contraction factor, so that the cells could not perform blastocyst contraction, and found that the aspect ratio of the embryonic cell during the same period dropped by 43%, the eccentricity dropped by 10%, and the microtubule standard deviation increased by 45%. Microtubule deviation increased by 141%. They also transfected the Gal4 promoter into the cells to pro- mote apoptosis and change the morphology of the cells. They found that the aspect ratio of the cells decreased by 26%, the eccentricity decreased by 4%, and the standard deviation of microtubules increased by 14%. The above changes are the changes that occur only after the cell morphology changes, not the changes brought about by gene mutations. Subsequently, they completely destroyed the intracellular microtubule structure by making the cell ex- press the microtubule shearing protein spastin, and found that the morphology of the cell did change (P=0 02), but the degree is lighter (the aspect ratio is reduced by 25%, and the eccentricity is reduced by 1%).

The structure of microtubules in the cell is constant- ly undergoing the conversion of depolymerization and repolymerization. This process is called microtubule dynamics. Depolymerization is the transformation of micro- tubules from growth to shortening, and repolymerization is the transformation from shortening to growth. Previous studies believe that microtubules are constantly damaged during the aging process and are more prone to disaggregation. Recent studies have shown that depolymerization is easy to occur at the positive end of the microtubules that are initially formed. However, once the positive end begins to extend, the ability to disaggregate rapidly declines. The process of depolymerization and repolymerization of microtubules is affected by microtubule-associated proteins (MAPs) and motor proteins. MAPs include microtubule structure-related proteins, microtubule positive

end tracer proteins and so on. Microtubule structure related proteins include MAP1, MAP2, MAP4 family and Tau protein. They are called structurally related proteins because they do not exist.

The enzyme activity is only bound to the surface of the microtubules, thereby enhancing the stability of the microtubules. The positive end of the microtubule tracer protein specifically acts on the growth end of the microtubule and regulates the growth of the microtubule. Early re- search believed that microtubule structure-related proteins are mainly distributed in the nervous system and perform physical functions. MAP1 is divided into three subtypes: MAP1A, MAP1B, and MAP1S. MAP1A and MAP1B are mainly distributed in neurons and play a role in guiding the formation of axons; MAP1S is widely expressed in cells and regulates cell division and autophagy. MAP2 is the highest content of neurotubule associated protein. It exists in the entire neuron in the early developmental stage of the neuron. Then MAP2 in the axon disappears and only exists in the dendrites. MAP4 is distributed in a variety of cells and also plays a role in stabilizing the structure of microtubules. Tau protein can promote the polar formation of neurons.

With the elongation of axons, the abnormality of Tau protein can lead to many kinds of neurodegeneration Lesions. In recent years, it has been discovered that in addition to affecting microtubule motility, microtubule structure-related proteins may also be related to the occurrence and development of tumors. Tessema et al. screened the methylation level of gene promoters on 117 frozen case specimens of non-small cell lung cancer, 5 human bronchial epithelial cell lines, 5 human small airway epithelial cell lines, and 23 non-small cell lines. It was found that the CpG island of the promoter of the MAP1B gene has a significantly higher methylation ratio in tumor tissues, and the methylation ratio is higher in the case of COPD (combined 68%, not 37%), and the tumor gene map project. The information in the database matches. However, there is no difference in the expression level of MAP1B in tumor tissues and non-tumor tissues. Therefore, the expression of MAP1B is related to tumor transformation, but the specific mechanism remains to be further studied. Bauer et al. collected pathological specimens of breast cancer patients who underwent surgical treatment after paclitaxel adjuvant chemotherapy, extracted total RNA from 14 cases and performed gene chip analysis, and found that in the cases of complete pathological remission, the expression of MAP2 gene was higher than that of incomplete remission. The number of cases is 4 times higher. They collected MAP2 mRNA in 5 breast cancer cell lines and found that the expression of MAP2 was highly correlated with paclitaxel sensitivity in vitro (correlation coefficient R2>0 99). Later, they used two groups of breast cancer cell lines MCF-7 and MDA-MB-468 to overexpress MAP2, and the two groups of cell lines were treated with paclitaxel and found that the number of cells decreased by 53 7% and 46 4%, respectively. In addition, in 47 needle biopsy cases, patients with high MAP2 expression had a higher percentage of complete remission. Therefore, MAP2 can play a synergistic effect with paclitaxel and can be

used as a biomarker of paclitaxel sensitivity. This may be related to the effect of both MAP2 and paclitaxel on microtubules, which promotes cell cycle arrest in G2/ M phase. Yang et al. used Westernblot and real-time quantitative polymerase chain reaction to detect the Tau protein in three prostate cancer cell lines, and found that two of them had expression. Subsequently, they cultured the two cell lines into docetaxel-resistant cell lines and found that the expression of Tau increased, and the expression of Tau was positively correlated with the PI3K/Akt/mTOR pathway. In addition, silencing the wild-type and drug-resistant strains of Tau inhibited the growth of tumor cells and increased the sensitivity to docetaxel. Therefore, Tau can play an antagonistic effect with paclitaxel and can be used as a biomarker of docetaxel sensitivity, which may be related to the competition between Tau and docetaxel for the binding site of microtubules. The above results all suggest that microtubules are related to the occurrence, development and treatment of tumors, but further research is still needed to reveal the relationship between the two.

3.The Structure and Function of Microfilaments and Tumor Cell Infiltration

Microfilaments are solid filamentous structures with a diameter of 5-7nm, which are distributed in the cytoplasm and nucleus of most cells, but myofilaments in the cytoplasm of the cells are the most developed. Long and short filaments are connected to each other and surround all organelles. Microfilaments can exist in the form of mono- filaments, or form a network, or they can exist in bundles. Actin is the main component of microfilaments, and it exists in two forms in the body: actin monomer (G-actin, also known as globular actin) and fibrous muscle assembled from actin monomers F-actin. Among them, the actin monomer is a globular protein with a molecular weight of about 43kDa, which is divided into three types: α, β, and γ according to the isoelectric point. The complex intracel lular cytoskeleton network composed of microfilaments and their related regulatory proteins participates in most of the biological behaviors in life. In malignantly trans- formed cells, cells often show the destruction of cytoskeleton and abnormal aggregation of microfilaments. The infiltration and metastasis of tumor cells are related to the changes in the expression of microfilaments and related proteins. The abnormal aggregation of microfilaments can enhance the mobility of tumor cells.

In order to clarify the functions of various actins, researchers have established different types of knockout mice. Kumar et al. tried to establish α-cardiomyocyte type knockout mouse models. The mice died during embryonic or perinatal period, and the myocardial fibers were severely disordered, suggesting that α-cardiomyocytes are closely related to the formation of cardiomyocytes. Crawford et al. established the α-skeletal muscle type gene knockout mouse model and found that their skeletal muscle function is very weak, and they all died on the 9th day after birth, suggesting that the α-skeletal muscle type is necessary for muscle contraction. Schildmeyer et al. established an α-smooth muscle type

gene knockout mouse model and found that the expression of α-skeletal muscle type was increased compensatoryly, although the cardiovascular system of mice developed normally. However, the vasoconstriction ability becomes weaker, the blood pressure is lower than that of normal mice, and the blood flow rate becomes slower, suggesting that α-smooth muscle type regulates vasoconstriction, which is closely related to arterial tension and the activity of myofibroblasts. Kumar et al. overexpressed the γ-smooth muscle type gene in α-cardiomyocyte type knockout mice, and some mice survived, but when they became adults, symptoms such as cardiac insufficiency and myocardial hypertrophy appeared, suggesting that γ-smooth muscle type could be partially replaced. The role of α-cardiomyocytes in cardiomyocytes. Shawlot et al. tried to establish a β-cytoplasmic sub-equivalent gene mouse model, all of which died of non-specific exhaustion early in life, suggesting that the β-cytoplasmic type is necessary for cell survival. Belyantseva et al. established a γ-cytoplasmic knockout mouse model and found that these mice are thinner than wild-type or heterozygous types in the early developmental stage, and some can survive to adulthood and are fertile, but a large part of them are due to development. Delayed death, and some random deaths in adulthood, suggesting that γ-cytoplasmic type is related to growth and development. In the cell, actin is divided into two forms: monomericactin (G-actin) white monomer and filamentous actin (F-actin) polymer. F-actin is a long-chain fiber composed of multiple G actins, and two F-actins are combined in anti-parallel to form a spiral chain, which exerts physiological functions. The nucleotide binding site of each molecule of G-actin binds to one molecule of ATP and connects with one Mg2+ or Ca2+ to form an actin ATP-divalent cation complex. When G-actin is combined with F-actin, ATP is hydrolyzed to ADP, which provides energy for the process.

Actin is widespread in eukaryotic cells. In most cells,β-cytoplasmic type:γ-cytoplasmic type is about 2:1. How- ever, in different cells, this ratio will change. For example, the mouse testis is 1:1, the liver is 25:1, and the aorta is 6:1. The content of actin also changes with changes in pathological processes, and the β-cytoplasmic type is of- ten highly expressed in aggressive tumors, such as aggressive colorectal cancer and murine sarcoma virus-transfeced MDCK cells.

Cells or melanoma T1C1 cells. Simiczyjew et al. overexpressed β-cytoplasmic and γ-cytoplasmic type in human colorectal adenocarcinoma LS174T cell line and found that the ratio of F-actin to G-actin increased, indicating the degree of actin polymerization increased, and observed under a phase-contrast fluorescence microscope, the vesicles of the cell membrane grow actively. The above results all suggest that the increase of actin content can enhance the exercise ability of tumor cells.

Cell movement is closely related to the formation of cell membrane protrusions. Moving cells will protrude two kinds of pseudopods at the front, namely filopodia and lamellopods. The formation of pseudopodia relies on the formation of actin microfilament skeletons under the cell membrane. In lamellipodia, G-actin aggregates into F-actin, and F-actin forms a cross branch network; in filament pseudopodia, F-actin forms

a parallel bundle structure. Cell movement is relying on pseudopodia to crawl. The formation of pseudopodia is mediated by Rho family GTPase. The formation of lamellipodia is mediated by Rac1 protein, and the formation of filopodia is mediated by Cdc42 protein. Chen et al. analyzed the expression of Rac1 in 150 cases of lung cancer tissues and 30 cases of adjacent lung tissues, and the expression of Cdc42 in 110 cases of lung cancer tissues and 30 cases of adjacent lung tissues. The results showed that Rac1 was expressed in 94/150 (62 67%) of lung cancer tissues, and almost not expressed in lung tissues adjacent to cancer; Cdc42 was expressed in 80/110 (72 73%) of lung cancer tissues, and almost expressed in lung tissues adjacent to cancer.

Almost not expressing. The expression levels of Rac1 and Cdc42 are significantly positively correlated with lymph node metastasis, TMN staging and pathological differentiation. The five-year survival rate of Rac1 negative patients is 32 14%, and the five-year survival rate of positive patients is 17 02%; the five-year survival rate of Cdc42 negative patients is 36 67%. The positive rate is 13 75%, indicating that the occurrence, development and prognosis of Rac1 and Cdc42 tumors are closely related. In cell experiments, they used scratch experiments and in- vasion tests to confirm that the expression levels of Rac1 and Cdc42 are positively correlated with the motility of cells. After being stimulated by epidermal growth factor,Rac1.

Darby grows more lamellipodia than Rac1 silenced cells, and this process is effected through the Rac1-Pak1 pathway; Cdc42 expresses more filopodia than Cdc42 silenced cells. When the expression levels of Rac1 and Cdc42 are down-regulated, tumor cells are less resistant to anti-tumor drugs such as nedaplatin and curcumin.

Increased sensitivity. The above results all indicate that the expression level and distribution of actin filaments affect the migration and invasion of tumor cells, and the regulatory factors related to filaments may be a new target for tumor treatment.

4.The Structure and Function of Intermediate Filaments and Tumor Cell Infiltration

Intermediate filament (IF) exists in the cell cytoplasm and is a tubular structure with a diameter of about 8-11 nm. Because its diameter is between microfilament and microtubule, it is called intermediate filament. The composition of the intermediate filament is more complicated than that of microtubules and microfilaments. Intermediate filaments are composed of intermediate filament proteins. According to different biochemical characteristics such as immunological and electrophoretic properties, intermediate filament proteins can be divided into five types: cytokeratin, flexible paper-like protein, intermyolin, and glial fibril fibrils. Acidic protein, nerve filament. The expression of intermediate filament protein in tumor cells is closely related to the degree of differentiation of tumor cells.

5.The Importance of the Cytoskeleton System to the Infiltration and Growth of Tumor Cells

Human malignant tumor cells, especially tumor cells that are located around the tumor and infiltrate the surrounding tissues, have pseudopod like cytoplasmic protrusions, well-developed microfilament meshes inside, and increased filamentous actin aggregates of microfilaments. It is easy to interact with myosin and cause contraction, which is of great significance to the movement and invasive growth of cancer cells. In the process of tumor cell movement, microfilaments are the most important structural skeleton that constitutes the lamellar pseudopodia of the motor cells, and the adhesion bands and adhesion plaques are the physical connections between the extracellular matrix and the stress fibers formed by the micro-filaments in the cells. The coordinated aggregation of multiple microfilaments can generate a prominent force on the cell surface, drive the extension of the plasma membrane at the front edge of the cell to form pseudopodia, and pro- mote the movement of tumor cells. In breast cancer, the actin related protein ARP2 and WAVE2 are co-expressed, which affects the structure of microfilaments, increases pseudopodia, and enhances cell motility. It is closely related to the invasiveness of breast infiltrating ductal carcinoma cells, so it can be used as one of the prognostic indicators of invasive breast cance.. After the fascin is inhibited, it can block the production of filopodia , reduce the nuclear movement and deformability of tumor cells, thereby inhibiting the migration and invasion of tumor cells. Zhang Hongying, Yang Guanghua et al.studied the relationship between the cytoskeleton and three different human rhabdomyosarcoma cell lines with different metastatic potential and found that the number of microfilaments and microtubule skeletons in rhabdo myosarcoma cells is reduced and dysplasia. The potential is negatively correlated ($P<0.05$); the frequency of actin bodies is positively correlated with the metastatic potential of rhabdomyosarcoma ($P<0.05$); there is no obvious abnormality in the structure of intermediate filaments in rhabdomyosarcoma, and there is no difference in fluorescence intensity between the two significance ($P>0.05$), it is concluded that the abnormality of the cytoskeleton of different degrees may be related to the different infiltration and metastasis potential of rhabdomyosarcoma, and it may become one of the indicators for judging the malignancy and prognosis of rhabdomyosarcoma. Lu Rui, Ke Yang and other studies on human gastric cancer cell line BGC-823 showed that the microfilament skeleton assembly state in tumor cells is negatively correlated with the ability of infiltration and metastasis.

6.Summary

The current research has a relatively systematic and clear understanding of the cytoskeleton system. The growth and infiltration of tumor cells is a multi-stage process and is closely related to the complete microtubule system in the cell. We still lack effective treatments to inhibit the infiltration and growth of tumor cells. The close connection between the cytoskeleton system and the infiltration and growth of tumor cells can provide new ideas for the treatment of tumors.

Funding

(1)The second batch of Chinese medicine clinical research bases in China

Number: 2018

Source: State Administration of Traditional Chinese Medicine

(2)The prevention and treatment of tumor complications and the leading team of Chinese medicine research and development technology

Number: 2020TD04

Source: Shanxi Provincial Health Commission

(3)Exploring the effect of Huangqi Liuyi Decoction on the 5-FU treatment of colon cancer model rats based on the immune regulation mechanism

Number: 2019PY-015

Source: Shanxi University of Traditional Chinese Medicine

(4)A clinical study on the treatment of colorectal cancer with liver metastasis of Qi deficiency syndrome by the method of invigorating the middle and replenishing qi combined with chemotherapy-a randomized, parallel con- trolled, multi-center clinical study

Number: 201903D321225

Source: Shanxi Provincial Department of Science and Technology

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Hemichorea Associated with Non-ketotic Hyperglycemia: A Case Report and Review of the Literature

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ABSTRACT

Hemichorea associated with non-ketotic hyperglycemia (HC-NH) is a rare disease. The purpose of this case report is to introduce a patient with HC-NH and provide a schedule of examination and follow-up treatment. We also reviewed the current understanding of pathophysiology and treatment and how to apply it to our patients. The case involved a 37-year-old Asian diabetic man who had a 9-day history of losing movement in left limbs and face. His initial blood glucose level was 10.13 mmol/L. HbA1c was 13.6%. Before admission, head CT scan showed suspicious small pieces of left brainstem with slightly high-density shadow and right putamen nucleus with high-density shadow. On the day of admission, head MRI showed punctate T1WI low signal shadow, T2WI high and low mixed signal shadow, T1WI high signal shadow and T2WI low signal shadow of right putamen nucleus. The case findings were consistent with his displayed motor pattern and with the HC-NH diagnosis. Gradual control of the blood glucose levels alleviates his choreiform symptoms. The endocrinology follow-up 6 months after discharge found that his symptoms did not recur after the outpatient's medication compliance was improved. HC-NH is a rare manifestation of poor diabetes control, but it should also be noticed by clinicians. Early recognition and gradual treatment of elevated blood glucose levels seem to completely alleviate choreiform symptoms.
Keywords: Chorea;Diabetes mellitus; Nonketotic hyperglycinemia

1.Introduction

Chorea is brief, quasi-purposeful, irregular muscle contractions, not repetitive or rhythmic, but flows from one muscle to the next and athetosis is slow, writhing,continuous movements of distal extremities (chiefly the fingers). Metabolic causes have been documented earlier, not worthy of that being Diabetes. Choreoathetosis has been reported earlier in elderly women. We now report a case of hemichoreoathetosis in an Asian male diabetic.

2.Case Presentation

A 37-year-old Asian male presented to our hospital on 29 May 2017 with a 9-day history of acute-onset choreoathetoid movements affected his left limbs and facial muscles. As explained by the patient, the movements were persistent, aggravated with mental strain, and disappeared during sleep. It prevented him from performing

his normal daily activities. His medical history included hypertension and weakness in the right limbs from a brainstem hemorrhage which occurred approximately six months prior to the current presentation. He had been diagnosed with diabetes mellitus half a year ago, but was not on any treatment. There was no other relevant past history and family history. The patient had prescriptions for Nifedipine, Irbesartan and Arotinolol. He was not taking any anti-psychotic or anti-seizure medications.

On physical examination, he was revealed to be conscious, had slurring of speech and had repetitive shrugs and rapid swing of his left limbs with no limb weakness, nystagmus or other cerebellar signs. Due to which, the heel-knee-tibia test and finger-nose test could not be performed accurately on his left side. The rest of the nervous system examination was normal.

Common causes of chorea in adult (Sydenham chorea, chronic progressive chorea, acanthocytosis, neoplastic disorders, ischemic or hemorrhagic stroke, and drug toxicity) were considered and were ruled out by appropriate investigations. On admission, his vital signs were as follows: height, 174 cm; weight, 74 kg; blood pressure, 138/92 mmHg; pulse rate, 72 beats/min;and body temperature, 36.6 ºC. No abnormal chest or abdominal findings or edema in his lower extremities were identified on a physical examination. On a laboratory examination, his blood urea nitrogen, and creatinine levels were all elevated. Laboratory examinations on admission showed poorly controlled diabetes mellitus. His fasting blood glucose and hemoglobin levels were 10.13 mmol/L (normal range:3.9-6.1) and 13.6% respectively, urine glucose (++++), and urine ketone (-)(see Table). Renal function tests revealed renal insufficiency. Full blood count, liver function tests, inflammatory markers, thyroid function tests, myocardial enzymogram, blood coagulation, immune index, homocysteine, urine protein electrophoresis, anti-neutrophilic cytoplasmic antibodies and electrocardiogram were normal. A cranial CT scan (29 May 2017) revealed a hyperdense area in the right putamen but no evidence of any acute intracranial pathology (see Figure 1). Brain MRI on day 1 showed high signal intensity on T1-weighted images and low signal intensity on T2-weighted in the same region in addition to the old hemorrhagic sequel lesion. This finding is classic for hyperglycemia-induced hemichorea syndrome.

Based on the above results, the hemichorea induced by the diabetic nonketotic hyperosmolar state was diagnosed. He was started on insulin and good glycemic control was achieved on day 4. The clinical improvement of his condition was correlated to better hyperglycemic control. A week later, the abnormal movements disappeared completely. The patient refused to have a follow-up brain MRI. During his 6 months of follow-up, the patient's blood sugar level was 10 mmol/L and chorea did not recur.

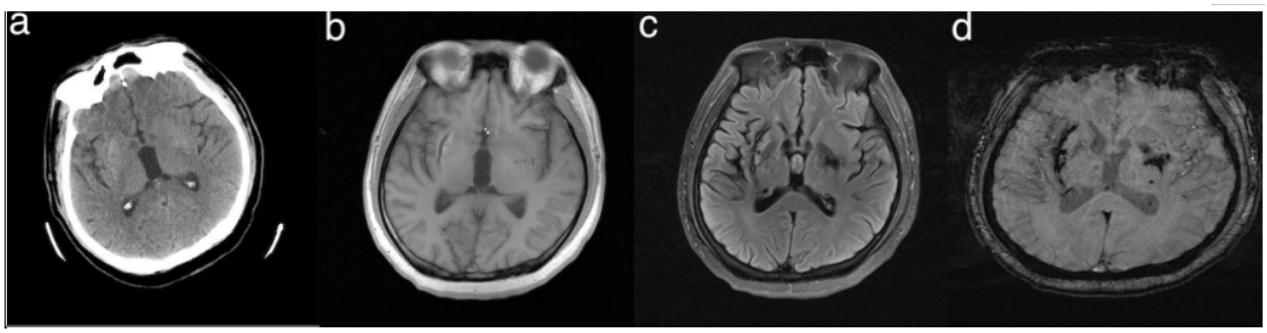

Figure 1. a: Cranial CT shows slight hyperdensity of the right putamen; b: MRI T1-weighted image shows remarkable hyperintensity of the right putamen; c: MRI T2-weighted image shows heterogeneous hyperintensity of the right putamen; d: SWI shows slight hyperintensity of the lesion

Table 1. Laboratory Findings on Admission

Hematology and biochemistry			
WBC	6.46×10^9 /L	BUN	15.37 mmol/L
RBC	4.1×10^9 /L	Cr	273.7μmol/L
Hb	125g/L	Na	140.0 mmol/L
Plt	155×10^9 /L	K	4.5 mmol/L
Tp	61.6 g/L	CL	110 mmol/L
T-Bil	16.7 μmol/L	CK	289 U/L
AST	30.7 U/L	Amy	98 IU/L
ALT	28.3 U/L	NT-pro BNP	187 pg/mL
LDH	235 U/L	Glu	10.13 mmol/L
ALP	81.9 U/L	HbA1c	13.6 %
γ-GTP	52.1 U/L	eGFR	46 mL/min/1.732
ChE	5.8 U/L	D-dimer	1.3 μg/mL
Urinalysis: pH 5.5 Glucose (++++)Protein (-) Occult blood (-)Acetone body (-)			

3.Discussion

Hemichorea associated with non-ketotic hyperglycemia (HC-NH) is a rare movement disorder which was first described in 1960 [1]. It is observed in type 2 diabetes and is very rare in patients with type 1 diabetes and diabetic ketoacidosis (DKA). It occurs predominantly in elderly diabetics with unsatisfactory blood glucose control, and women more often than men [2], which could be related to an underlying genetic predisposition [3]. In a meta-analysis of 53 patients [4], mean age was reported as 71 years, while male to female ratio was 1:1.8. A systematic review included 286 patients showed that women and non-ketotic hyperglycemia (NKH) patients were the most frequently affected (63% and 92%, respectively) [5]. Chorea is a relatively uncommon neurological manifestation of diabetes mellitus. Chang CV et al. [6]. Reported 3 cases of new-onest chorea-ballism induced by NKH, highlighting that chorea may be the first manifestation of undiagnosed decompensated diabetes mellitus.

Most patients with chorea associated with NKH have acute or subacute limb involuntary movement (more common on one side), and sometimes involuntary movements of facial muscle, chin, and tongue, accompanied by

severe increase in blood glucose and negative ketones in urine. The typical manifestation of NKH chorea is triad: non-ketotic hyperglycemia, hemichorea, and basal ganglia shows high signal in MRI T1 scan or high density in CT scan [7]. In examining this patient, we regarded this as a case of HC-NH due to the unilateral choreoathetotic movement, hyperglycemia on presentation with poor glycemic control, and absent urine ketones, contralateral T1 hyperintensity in the putamen with no restriction on the ADC map, and the absence of other metabolic derangements.

In general, diabetic lateral chorea caused lesions in the striatum [8]. The development of putamen lesions is unchanged, and there are similar lesions are observed in globus pallidus and caudate nucleus. Neurodegenerative diseases that cause basal ganglia injury include Huntington's disease, spinocerebellar degeneration, such as dentatorual pallidoluysian atrophy, and Creutzfeldt- Jakob disease, which involves elevated ubiquitin levels. These two neurological diseases are progressive in nature, and the treatment has not been determined. These diseases were also excluded because the patient's symptoms improved. Globus pallidus lesions can also be caused by carbon monoxide poisoning; in this case, the lesion shows low signal intensity on T1-weighted images. Other diseases particularly associated with diabetes include mitochondrial diseases, Stiff-syndrome caused by decreased GABA activity, and myoclonus caused by muscular atrophy of diabetes. The 3243 point mutation in mitochondrial DNA nucleotide sequence is associated with family history of diabetes, and is also observed in mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes (MELAS). It is reported that there is ataxia in MELAS with diabetes mellitus. MELAS showed cerebral infarction like lesions in the occipital region. Stiff-person syndrome is characterized by epileptic muscle spasm in the muscles of the trunk and proximal limbs, which spreads to the whole body within a few months. In our patients, involuntary movement was only present in the left upper and lower limbs; Therefore, Stiff-person syndrome was also excluded.

There are characteristic radiographic manifestations under normal circumstances: the contralateral striatum in MRI T1-weighted show high signal changes and equal or low signal in MRI T2-weighted, mostly high-density changes in head CT [9]. The radiological abnormalities are completely reversible[10]. Despite characteristic imaging findings and clinical manifestations, the underlying mechanism is still unclear. Positron emission tomography (PET) studies were performed in 3 patients at 3 weeks, 5 weeks, and 7 months after clinical onset, showed the markedly reduced rates of cerebral glucose metabolism in the corresponding lesions on MRI T1-weighted[11]. Additionally, proton MR spectroscopy (MRS) was performed and revealed a decreased N-acetylaspartate/creatine and N-acetylaspartate/choline ratio, indicating neuronal damage of the contralateral putamen [12]. Findings of the patients' brain have produced an argue about the pathology. In our patient, we can find the contralateral T1 hyperintensity in the putamen. The putamen showed multiple foci of recent infracts

associated with interneuronal response and reactive astrocyte. This suggests a reaction to microinfraction. But histologic examination of the cerebral tissue was obtained some time. There was no blocked vessels. Therefore, histological studies related to brain MRI results are still inconclusive. This requires further research through pathological studies including a large number of patients.

In addition, as mentioned above, few patients have a negative performance on MRI or CT scan. Most patients with this condition have a good prognosis. Controlling blood glucose is the most important treatment. With the decline of blood glucose level, some patients' involuntary movements can be alleviated. To date, only a few negative imaging cases have been reported by other researchers [13]. According to the current reported cases, we believe that the syndrome can be divided into 2 types: diabetes, ketone negative, hyperglycemia, unilateral or bilateral chorea, while typical imaging changes in head MRI or CT scan are the most common type, and diabetes, hyperglycemia, ketone negative, unilateral or bilateral chorea and negative imaging changes are relatively rare types. We wish to emphasize that NKH chorea with normal imaging can represent a subtype, although this subtype is not common.At present, the specific mechanism of NKH chorea is not clear. The possible mechanism is that when hyperglycemia occurs, the metabolism of brain cells gradually changes to anaerobic metabolism due to the decrease of local cerebral blood flow and the failure of glucose metabolism. Then γ-aminobutyric acid (GABA) has become the main energy source of brain cells. Acetoacetic acid from ketosis patients can be used to synthesize GABA. GABA in patients with non-ketotic hyperglycemia is rapidly depleted due to lack of acetoacetic acid, so the normal activities of basal ganglia are impaired [14]. Scine patients with NKH are prone to chorea.

The pathophysiology of chorea remains to be fully elucidated, but it is believed that it involves the destruction of the balance of neural network activities between the motor cortex and the basal ganglia, including metabolic disorders or structural damage in the subcortical nucleus, caudate nucleus, subthalamic nucleus and thalamus. Potential pathogenetic mechanisms include relative dopaminergic hypersensitivity, impaired synthesis of acetylcholine or gamma-aminobutyric acid, or an undefined effect of hyperosmolarity, perhaps unmasking a previously subclinical lesion of the basal ganglia.In previous studies, typical sites of hemichorea included subthalamic, striatum and basal ganglia [15]. Functional imaging revealed neuronal loss and dysfunction in many chorea syndromes, as well as changes in metabolism and presymptomatic dopaminergic dysfunction [16].

Because there are many causes of chorea, the treatment is very challenging. Doctors should collect comprehensive medical history, including medication history of potential pathogens and recent history of streptococcal infection, and examine the nervous and mental systems of patients with symptoms [17]. Neuroimaging, gene detection and laboratory examinations can confirm the suspected diagnosis of chorea. Mild chorea may not need treatment[18] Primary chorea can be treated with dopaminergic

antagonists, including antipsychotics; However, side effects including Parkinson's disease and delayed syndrome [17]. Dopamine depletors that inhibit presynaptic dopamine release and block postsynaptic dopamine receptors are effective, especially in combination with dopamine antagonists [17]. In the treatment of secondary chorea, the main etiology should be solved. In diabetic chorea, blood glucose control should be optimized. If chorea is caused by drugs or toxicity, the pathogen should be withdrawn. Drugs for the treatment of primary chorea can be used to treat the symptoms of secondary chorea [17]. Surgical treatments such as pallidotomy and deep brain stimulation may also be an option [18].

However, not all HC-NH patients can prove this theory through extensive investigation, because of the cost of investigation, such as MRI. In this case, the most likely diagnosis can be obtained using clinical sensitivity and appropriate diagnostic methods. For this patient, combined with clinical history and investigation, other common causes of hemiplegia were excluded. A brain CT scan was performed to rule out other potential risk causes, such as stroke. MRI is undoubtedly the best diagnostic method; however, in some cases, this is not allowed due to accessibility and cost. Nevertheless, it should not be a limiting factor for primary care doctors to make this diagnosis. Other clinical aspects of medical history and clinical findings can also be used to help diagnose. Due to the elusive nature of this report, clinicians can easily miss it. Therefore, clinicians must be vigilant and keep in mind that such abnormal exercise may occur in patients with poor long-term blood glucose level control, especially in the elderly in Asia. Patients need to be hospitalized for blood glucose normalization, and other potential causes must be excluded. Usually, once the blood glucose level drops to the normal range, abnormal exercise disappears or decreases significantly. However, complete remission varies within days, weeks and months after blood glucose normalization. In some cases, abnormal exercise may last more than a year.

Although this Hemichorea secondary to hyperglycemia is benign and usually has a good prognosis, it has a great impact on patients and their families. Because of this abnormal movement, patients feel disabled and painful, because most of their basic activities take longer to complete, and they need the help of other family members. This has also brought heavy losses to the families. In these cases, it is important to recognize the underlying causes, because correcting potential hyperglycemia usually can quickly alleviate the symptoms. Therefore, clinicians should be resourceful in dealing with patients' biological, psychological and social problems. This case demonstrates that uncontrolled diabetes can be seen as a rare disorder of movement. Being unfamiliar with these situations may lead the attending physician to attribute them to psychological or mental disorders. For all primary care doctors dealing with this common medical problem, a high degree of doubt is necessary.

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The Application of Block Chain Technology in Medical Management

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ABSTRACT

With the gradual development of social economy, the social function of medical institutions is becoming more and more important. Strengthening the efficiency and quality of medical management can alleviate the contradiction between doctors and patients and improve the level of medical service. Promoting the sustainable development of medical institutions plays a key role. Under the background of the development of science and technology, the theoretical research and practical application of block chain technology are becoming more and more mature, which can not only store and transmit information effectively, but also strengthen the security of information storage. The effective combination of block chain technology and medical management can create a new operation mode and train of thought for medical management and promote the overall improvement of medical management quality and efficiency. It is very helpful to optimize the social service function in medical field. This paper mainly expounds and probes into the concept characteristics of block chain technology, its concrete application in medical management, application effect control strategy and so on. It aims to further strengthen the depth and breadth of application of block chain technology in medical management, provide strong power support for the improvement of medical management service level and promote the sustainable development of medical and health industry.

Keywords: Blockchain technology;Medical management;Information;Application

1.Introduction

The function of medical institutions in social development is increasing, the business is increasing gradually, and the pressure of medical management is also increasing day by day. It is necessary to optimize and innovate the traditional medical management mode. In order to meet the high demand of medical management in the new period, block chain technology is a decentralized distributed record and storage database.

2.Overview of Blockchain Technology

(1)Concepts and characteristics

Block chain technology is a decentralized distributed bookkeeping technology. By constructing a database, th e related data are recorded and stored distributed, and different blocks are effectively combined by using the chain mode. In forming a systematic data structure system, block chain technology has the

characteristics of non-tampering, traceability, openness, security, data recording sequence and so on. It can not only guarantee the privacy and security of data, but also share data, so that participants can reach a consensus on data sequence, security, sharing, maintenance and so on. These characteristics of block chain technology, it strengthens its decentralization and detrust application core, and simplifies the process of data application. In general, block chain technology is a distributed linked account book, and it is encrypted and managed by complicated cryptography to ensure that the account data can not be tampered with, and all the data in the account book can be traced back.

(2)Characteristics of application of blockchain technology in medical management

The block chain can generate large data for each link of medical service management, such as medical record information, hospital internal information, drug use information and so on, and cause non-tampering, and ensure the security of its data information. The main application features are as follows: using the decentralization of block chain, combining cloud storage technology, expanding the storage space of medical information, and realizing seamless connection and sharing of information data; using public-private key consensus mechanism the anonymity and confidentiality of data information in the sharing process, and strengthening the privacy security of medical management information.

3.Problems of Medical Management in the Context of Information Technology

At present, the process of medical information management informatization is not very ideal, which seriously affects the improvement of its comprehensive level of informatization and limits the improvement of the efficiency of medical service industry in China. The main performance is: medical information sharing is difficult to achieve, due to the lack of unified block chain technology application standards and norms, many medical institutions hold a wait-and-see attitude, and in their own interests, there is resistance to information sharing; Lack of perfect medical service management quality supervision mechanism, leading to medical service quality problems, serious doctor-patient contradictions, seriously affect the healthy development of China's medical industry; The traditional medical insurance claim process is more cumbersome, inefficient, time-consuming, and the compensation results are prone to deviation and other problems, seriously reduce the patient's medical service experience, but also bring some obstacles to the sharing of medical information.

Application of blockchain technology in medical management

(1)Establishment of electronic health records

Using blockchain technology can establish personalized electronic health files for patients and store them in data sharing centers. When patients seek medical treatment, doctors can quickly and intuitively understand and view the patient's medical records, disease history and other information, and can use the traceability characteristics of block chain technology to trace the traces of medical activities received

by patients in the past. In the electronic health file, patients can also view their own examination results data, such as doctor diagnosis results, electrocardiogram, imaging and other data information, so as to have a clearer understanding of the condition and health planning. In addition, using the relevant functions of block chain technology, we can also make comprehensive encryption settings for electronic health files, which can not only share data, but also ensure data information security, let patients set their own access rights, and set up custom encryption methods to ensure patient privacy.

(2)Strengthening the whole process of drug supervision

Drugs play a key role in human health. Once drugs are made and sold, they will pose a serious threat to the life and health of patients. Therefore, the block chain technology can be used to track and record the production, sale, management and use of drugs dynamically, and the whole life cycle of drugs can be traced back as the main basis of drug market supervision. When patients buy and use related drugs, they can upload relevant data to the information sharing center and compare with the relevant information of the database constructed by blockchain technology, so as to identify and judge the truth and hood of drugs. Can not only protect patient life safety, but also strengthen drug market supervision and effect.

(3)Medical insurance claims

In the traditional medical insurance claim mode, the policyholder needs to go through many links and process- es to get the claim payment, in which he has to pay the medical expenses —— obtain the expense list —— the insurance company claims and so on. Because the claim company involves the problem of data information confidentiality in the process of docking with the hospital, the process is often complicated and long, time-consuming and inefficient. Under the background of block chain technology, it can effectively improve the efficiency and experience of medical insurance claims. This is because the block chain technology has the characteristics of non-tampering and traceability, which can record the trace of data change in detail and comprehensively, thus ensuring the security of data information. Based on this, a block chain platform can be constructed to store related information data distributed to enhance the comprehensiveness and security of data information. Moreover, the data information can not be tampered with to prevent the dispute over the related contract in the process of claim settlement, and through the effective fusion of block chain technology and artificial intelligence technology, the related cost information, contract and so on can be intelligently verified, thus providing the basis for the automatic execution of this process. The hospital and the insurance company jointly construct the intelligent contract block chain platform, form the data sharing account book, realize the medical insurance information sharing, simplify the medical insurance claim process, shorten the application time, improve the overall working efficiency of the medical management, and strengthen the medical service experience.

(4)Improving medical records of electronic operations The block chain technology is

used to record and store the surgical records comprehensively, and its non-tampering and traceability characteristics are used to ensure the authenticity of the original data, which is convenient to provide the basis for the investigation of medical malpractice responsibility and to clarify the relevant responsible persons.

4.Control Strategy for Application of Blockchain Technology

(1)To sum up experience and improve the promotion effect

The application of block chain technology in medical management started late, practical application experience is less, in the concrete application is still in the groping stage, the operation effect is affected to a certain extent. Moreover, the application of block chain technology poses a great challenge to the previous medical management model, and some medical institutions dare not apply it in depth, which leads to its promotion and application effect is not ideal. And in the domestic and foreign application, it has not formed the unified use standard and the basic standard. Many medical institutions adopt the wait-and-see attitude to it. Based on this, it is necessary to publicize blockchain technology in a wider range, strengthen people's overall understanding and understanding of it, and enhance their confidence in application. Build a good blockchain academic research atmosphere and environment, build a perfect blockchain medical management knowledge training system, strengthen the learning mo- tivation of medical managers, strengthen the academic interest of experts, and ensure the deep application of blockchain technology in medical management.

(2)Expansion of data storage space

The block chain database records and stores the dynamic changes of each data from generation to development, and it also takes up part of the space during the download, transfer, update and use of its data. Especially when the data of all nodes run synchronously, it brings great pres- sure to the storage capacity of the database. It is very likely that the medical information can not be updated in time because of the insufficient storage capacity, which affects the efficiency of medical management. Based on this, we should pay attention to strengthening the scalability and affordability of block chain database, optimize and perfect its decentralized storage system, expand its storage capacity, and build a decentralized business model in combination with specific conditions. Expand storage space and build a global scale of hard disk storage space.

(3)Enhanced data security

Because block chain technology runs under the back- ground of network information technology, even if it takes diversified encryption measures to ensure the security of block chain data, but because of the open characteristics of network technology, There are still some risks in data security and secret security. Based on this, we should optimize the key mechanism, improve the private key storage mode, strengthen its encryption effect, integrate the dynamic encryption technology and DES algorithm encryption technology, give full play to the functional advantages of complex cryptography. The access rights of users are

effectively controlled and block chain data are encrypted to ensure the privacy of medical data.

5.Conclusions

To sum up, with the trend of diversification of medical institutions, the quality and efficiency of medical management quality and efficiency of medical management. In combination with the concept and technical characteristics of block chain, we should explore the convergence of block chain technology and medical management, strengthen the effective combination of the two, give full play to the technical advantages of block chain, and carry out deep application in electronic health files, drug supervision, medical insurance claims, surgical information records, etc.

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