Clinical Trial Report for Medical Device

Name of testing device: Regenerative Dural Repair Patch

Clinical Trial of Regenerative Dural Repair Patch

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RDS-10/RDS-11

Clinical trial institutions: ZhuJiang Hospital of Southern Medical University, Wuhan General Hospital of Guangzhou Military, Renmin Hospital of Wuhan University, Tang Du Hospital of The Fourth Military Medical University

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Sponsor: Medprin Regenerative Medical Technologies Co., Ltd.

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1. Introduction

The dura is a layer of important structure on the surface of brain tissue, which is the barrier to protect brain. The importance of dura has been widely confirmed. In neurosurgery, the integrity of the dura is very important for brain surgery subjects, and the meningeal repair material play an important role in the reconstruction of the dura integrity, protection of brain tissue, and the prevention of complications such as cerebrospinal fluid leakage, intracranial infection, encephalocele, epilepsy, etc. Brain trauma, brain tumors, cerebrovascular disease, increase of cranial content volume, some congenital diseases, surgical procedure itself and other factors may cause the dura defect, which needs to use other alternative materials to repair the defective dura in order to maintain the integrity of the anatomical structure.

In recent years, the materials used to repair the dura mainly contain autologous fascia, allograft materials, dissimilar materials, natural and synthetic materials. Although there is no tissue compatibility issue, autologous fascia has limited source, easily leads to secondary damage and has poorer strength than dura. The allograft materials easily cause virus infection and rejection reaction [1] [2]. Heterogeneous biofilm has a risk of transmission of animal diseases. Due to the limitations of existing products, the concern about the development of new products is increasing at home and abroad.

The Regenerative Dural Repair Patch produced by Medprin Regenerative Medical Technologies Co., Ltd. is a synthetic dura with the application of regenerative medicine principle. This product adopts absorbable polymer material widely used clinically with a high degree of three-dimensional biomimetic structure, whch is in favor of the migration and growth of nascent cell, and accelerates the repair and growth of nascent meningeal. As the material is gradually degraded and absorbed in the body, nascent meningeal tissue gradually forms, so as to achieve the meaningful reconstruction.

The raw material of Regenerative Dural Repair Patch is a single component of medical polylactic acid. Polylactic acid is widely used in the field of medicine [3] [4], and its safety has been proven clinically [5] [6]. Dura mater patch (trade name: Ethisorb), a similar products with polylactic acid as the main raw material, has been widely used clinically, with no product-related adverse events. The safety and reliability has been demonstrated [5] [6].

Regenerative Dural Repair Patch is an artificial dural mater with three-dimensional reticular structure developed by bionic biotechnology in which medical polylactic acid is used as the raw material. Its basic structure is the nonwoven fabric-shaped film composed of micron grade fiber which is a white, flexible, pliable sheet with a thickness of 0.1-0.5mm.

Regenerative Dural Repair Patch has similar three-dimensional structure with dural mater matrix, which is in favor to the migration and growth of nascent cells, promotes the repair and reconstruction of the nascent meninx, and plays a role in protecting brain tissue and reducing postoperative complications. As a temporary repairing

material for dura defect, Regenerative Dural Repair Patch can not only repair the dura defect caused by cerebral trauma and brain tumors to maintain the integrity of dura anatomical structure and prevent the leakage of cerebrospinal fluid, but also can be absorbed and degraded postoperatively by the body, and substituted by autologous nascent tissues so as to avoid the long-term immune response caused by the presence of artificial dural mater and show a good histocompatibility.

According to the relevant provisions of the State Food and Drug Administration, before the new products put into the market, in order to confirm the safety and efficacy, clinical trials must be carried out [7]. Currently there are similar listed products in our country; therefore the test class is clinical validation [8].

This clinical trial is a multi-center, randomized, single-blind, parallel to positive control, non-inferiority design trial to verify the safety and efficacy of Regenerative Dural Repair Patch produced by Medprin Regenerative Medical Technologies Co., Ltd., and provide relevant basis for product registration.

The features of this product include are as following. It can close and reinforce the defective site of dura, and as a physical barrier it plays a role in the isolation of brain tissue and muscle, skull, scalp tissue. It can prevent infection and cerebrospinal fluid leakage to reduce postoperative complications. It has good tissue compatibility and no risk of virus infection and rejection reaction, and does not produce chemical toxicity reactions. Its mechanical properties meet the requirements of the surgical procedure, and it is easily to be tightly sutured with native meningeal tissue. It can be gradually degraded into non-toxic byproducts in the body, without long-term retention in the body. It has aseptic packaging for single-use sterilized by irradiation. It can be used directly after opening the package, without the need of cleaning and re-disinfection.

Preclinical files of this product: the preclinical type testing which has been completed according to the requirements has been detected by the State Food and Drug Administration, Jinan Medical Device Quality Supervision and Inspection Center, and a qualified inspection report has been issued.

Statement of compliance: this trial is in accordance with clinical trial protocol and the appropriate regulatory requirements in the regulations for clinical trial of medical device (directive 5).

2 Clinical trial objectives

To evaluate the safety and efficacy of Regenerative Dural Repair Patch produced by Medprin Regenerative Medical Technologies Co., Ltd. in dura defect repair surgery, and to observe possible complications of Regenerative Dural Repair Patch used as the material of dura repair surgery.

3 Clinical trial methods

This trial is a multi-center, randomized, single-blind, positive parallel control,

noninferiority validation clinical trial.

3.1 The subjects who met the inclusion criteria were enrolled in the trial according to the visiting time, and were performed preoperative inspection including blood test, liver and kidney function test, cell and humoral immunity examination.

3.2 The site, nature, size and incision of defect were observed intraoperatively.

3.3 The dura repair surgery was performed using appropriate size of test product or control product, which was sutured with surrounding dura stump by No.1 or No.0 silk. The skull was closed by conventional procedure.

3.4 The subjects were observed for fever, meningeal irritation, leakage of cerebrospinal fluid, subcutaneous effusion, nausea and vomiting, seizure, infections and scalp wound healing on the 1^{st}, 3^{rd}, 5^{th}, 7^{th} and 10^{th} day after the surgery. A lumbar puncture should be performed according to the condition 10±2 days after the surgery to measure the intracranial pressure and examine the situation of cerebrospinal fluid.

3.5 Blood test, liver and kidney function, cellular immunity and humoral immunity examination were performed 10±2 days after the surgery, and the values were recorded and compared with preoperative ones to evaluate the clinical significance. CT and clinical inspection were performed to examine the leakage of cerebrospinal fluid and subcutaneous effusion and to evaluate the relationship with test product or control product.

3.6 The subjects who need surgery at the same site or secondary brain surgery were observed for the situation of test product or control product on the repair site, such as adhesion with brain tissue, and histological examination was performed.

3.7 The subjects came back to visit the hospital on 90±10 days and 180±20 days after the surgery for the follow-up and were observed for fever, meningeal irritation, cerebrospinal fluid leakage, subcutaneous effusion , nausea and vomiting, seizure, infection and scalp wound healing.

4 Clinical trial contents

Subjects were inpatients neurosurgery department, with age of 18-65 years, male or female.

Main elements:

4.1 Effectiveness evaluation

4.1.1 Primary effectiveness evaluation indicators

Cerebrospinal fluid non-leakage rate: 10±2 days after the surgery, CT and clinical inspection were performed to confirm the presence of cerebrospinal fluid leakage and subcutaneous effusion.

4.1.2 Secondary efficacy evaluation indicators

4.1.2.1 Body temperature observation: on the 1st, 3rd, 5th, 7th and 10th day after the surgery, the subjects were detected for the change of body temperature, and the highest temperature of the day was recorded.

4.1.2.2 Scalp wound healing: on the 1st, 3rd, 5th, 7th, 10th day, 3rd month and 6th month after the surgery, the situation of scalp wound healing was reviewed.

4.2 Safety evaluation indicators

4.2.1 Cellular immunity and humoral immunity inspection were performed to determine if test product has immune reaction. The indicators of cell immunity include T cells (CD3+), absolute value of T cells (CD3) and CD4+/CD8+ ratio, and indicators of humoral immunity include IgA, IgE, IgM, IgG, CRP, C3 and C4.

4.2.2 Incidence of infection: the infection was determined according to the cerebrospinal fluid examination and clinical observation. The cerebrospinal fluid examination indicators include WBC, RBC, Glu, protein and chlorine.

4.2.3 Incidence of seizure

4.2.4 Blood test and liver and kidney function test: that if the change of each indicator in the blood test and liver and kidney function test is abnormal, and if abnormal change has clinical significance was recorded. The indicators in blood test include the number of red blood cell, hemoglobin, platelet, neutrophil, white blood cell and lymphocyte, and the indicators in liver and kidney function test include alanine aminotransferase, aspartate aminotransferase, globulin, albumin, total bilirubin, urea and creatinine.

5 Clinical general information

5.1 Trial Range: the patients in neurosurgery department with dura defect who need to implement the neurosurgery repair surgery.

5.2 Case selection

5.2.1 Inclusion criteria

5.2.1.1 Age of 18-65 years, male or female.

5.2.1.2 All the patients in neurosurgery department with dura defect who need to implement the neurosurgery repair surgery, including the patients with dura defect due to brain injury, brain tumor, cerebrovascular disease, congenital diseases of nervous system, posterior fossa surgery, intraspinal disease who need repair surgery.

5.2.1.3 Included patients had no obvious signs of infection before the surgery.

5.2.1.4 Included patients had no history of severe allergy and serious immunodeficiency.

5.2.1.5 The patient and/or the guardian agreed to participate in the trial, and signed the informed consent.

5.2.2 Exclusion criteria

5.2.2.1 The patients with disease of heart, liver, kidney, blood system or other vital organs.

5.2.2.2 The patients with unstable vital signs.

5.2.2.3 Pregnant or lactating women.

5.2.3 Case exclusion criteria

5.2.3.1 The subjects met exclusion criteria during the test.

5.2.3.2 Information missed or partially missed.

5.2.3.3 Other similar materials were used on the surgical site at the same time, or infection was developed due to other dissimilar implants.

5.2.3.4 Poor compliance.

Excluded cases should be explained for the reason, and no matter the efficacy analysis is done or not, the CRF form should be retained for future review. The subject has received one treatment and has safety records should be performed the safety analysis.

5.3 Calculation of sample size

his trial is a non-inferiority validation, with non-leakage of cerebrospinal fluid as the primary efficacy evaluation indicator, which belongs to a dichotomous qualitative indicator. Using professional software nQuery Advisor 7.0 for sample size estimation, the test performance (power) was set 80% with 0.025 as unilateral statistical significance level, and the number of cases was test group: control = 1:1 according to the balance design. Based on a comprehensive analysis on the data in published literatures, the cerebrospinal fluid non-leakage rate of control product and similar products was 95% [9], so the cerebrospinal fluid non-leakage rate of test product is also expected to be 95%. In addition, in accordance with the consensus from the investigators of this clinical trial and statistical experts, non-inferiority boundary value was determined as 12%, by which the sample size was estimated to be 52 cases for each group. Considering a dropout rate not more than 20% and the implementation of section randomization, finally the number of cases was determined as 66 cases for each group and totally 132 cases were required.

5.4 Number of cases

Enrollment: the 1st subject (No.001) was enrolled on Jun 27, 2011 at Center 01 Zhujiang Hospital, and the last subject (No.132) was enrolled on Jun 6, 2012 at Center 03 People's Hospital of Wuhan University.

Although only 3 centers were designed in this trial, actually Tangdu Hospital of the Fourth Military Medical University was added in this trial, and No.73-96 cases originally in Wuhan General Hospital of Guangzhou Military Region were included in Tangdu Hospital for the test.

132 cases were enrolled in this trial with 66 cases for experiment group and control group, respectively. 131 cases were included in MITTP (modified intent-to-treat population) for MITT analysis, with 66 cases in experiment group and 65 cases in control group. 117 cases were included in PPP (per protocol population), with 57 cases in experiment group and 60 cases in control group. 131 cases were included in SAP (safety assessment population), with 66 cases in experiment group and 65 cases in control group.

6 Test product and control product

6.1 Test product

Regenerative Dural Repair Patch developed by Medprin Regenerative Medical Technologies Co., Ltd., referred to as “test product”.

Name: Regenerative Dural Repair Patch (trade name: ReDura^{TM})

Manufacturer: Medprin Regenerative Medical Technologies Co., Ltd.

Specifications: RDS-1，RDS-2，RDS-3，RDS-4，RDS-5，RDS-6，RDS-7，RDS-8，RDS-9，RDS-10，RDS-11.

6.2 Control product

A positive control of Ethisorb Dura Patch (trade name: Ethisorb, Johnson & Johnson) was used in this trial, which has same action mechanism and indications with the test product, and has been listed for many years, referred to as “control product”.

Name: Ethisorb Dura Patch (trade name: Ethisorb)

Manufacturer: Johnson & Johnson Inter.C/O European Logistics Centre

Registration No.: SFDA (import) No. 2008 No. 3462482

Specifications: EDP23S, EDP23, EDP46S, EDP46, EDP614.

7 Statistical analysis methods and evaluation methods

7.1 Statistical analysis methods

7.1.1 Analyzed populations

7.1.1.1 Intent-to-treat population (ITTP)

Refers to all the patients with treatment intent and signed informed consent.

7.1.1.1 Modified intent-to-treat population (MITTP)

Refers to the patients who signed informed consent and completed the surgery with the record of corresponding efficacy indicators. Baseline data analysis was performed on MITTP. Efficacy analysis was based on the results of MITTP analysis.

7.1.1.3 Per-protocol population (PPP)

Refers to the patients who meet inclusion criteria, do not meet exclusion criteria, and completed the treatment protocol, i.e. the analysis (PP analysis) was performed on the patients with good compliance who completed required content in CRF. PP analysis was performed mainly for primary efficacy indicators.

7.1.1.4 Safety analysis population (SAP)

Refers to the patients with safety indicators, which was used for the statistical description and analysis on safety indicators and incidence of adverse reactions.

7.1.2 Statistical analysis methods

7.1.2.1 Statistical analysis software: SAS9.2 and IBM SPSS19 statistical software were used for the analysis;

7.1.2.2 Basic principles: two-sided test was used for all the statistical inference with defined test level of statistical significance of 0.05, and 95% confidence interval was used for confidence interval estimation of parameters;

7.1.2.3 Dropout analysis: Pearson χ^2 test was used for the comparison of total dropout rates and the dropout rates due to adverse events between the two groups;

7.1.2.4 Description of statistics: the measurement data were indicated with mean, standard deviation and confidence interval, if necessary, the minimum value, maximum value, P25, median and P75 were indicated; paired measurement data were also indicated with mean of difference and standard deviation; the median and mean rank were indicated when using non-parametric method. Enumeration data were indicated with frequency distribution and corresponding percentage. Ranked data were indicated with frequency distribution and corresponding percentage, as well as the median and mean rank. Qualitative data were indicated with positive rate, positive number and number of cases for the denominator;

7.1.2.5 Baseline data analysis of the two groups: descriptive analysis and deductive analysis were performed on baseline data (including demographic indicators, etc.);

7.1.2.6 Center effect analysis: the center effect was assessed by quantitative indicators with general linear model and qualitative indicators with Logistic regression;

7.1.2.7 Subgroup analysis: the subgroup analysis was not excluded for influencing factors possibly affecting the outcome variables.

7.2 Statistical evaluation indicators

7.2.1 Efficacy indicator

Primary efficacy indicators: validation of non- inferiority was performed. Qualitative variables: using 95% confidence interval for the difference of rate between test group and control group, non-inferiority of test group to control group was defined as the lower limit more than -12%. CMH test or logistic regression model was used for the evaluation of center effect.

Secondary efficacy indicators: quantitative variables: paired t test or Wilcoxon one-sample test was used for the comparison in the group; covariance analysis was used for the comparison between two groups, with corresponding baseline variables as covariant regression. Ranked variables: Wilcoxon one-sample test was used for the comparison in the group; logistic regression analysis was used for the comparison between two groups, with corresponding baseline variables as covariant regression.

7.2.2 Safety indicators

Safety Analysis: the incidence of adverse events in both groups was compared using Pearson χ^2 test, and the adverse events occurred in this trial were described in the list. The comparisons between groups and in the group were performed on quantitative indicators using corresponding tests for difference.

8 Clinical evaluation criteria

8.1 Efficacy evaluation criteria

8.1.1 Primary efficacy evaluation indicators

Cerebrospinal fluid non-leakage rate: 10±2 days after the surgery, CT and clinical inspection were performed to confirm the presence of cerebrospinal fluid leakage and subcutaneous effusion.

8.1.2 Secondary efficacy evaluation indicators

8.1.2.1 Body temperature observation: on the 1^{st}, 3^{rd}, 5^{th}, 7^{th} and 10^{th} day after the surgery, the subjects were detected for the change of body temperature, and the highest temperature of the day was recorded.

8.1.2.2 Scalp wound healing: on the 1^{st}, 3^{rd}, 5^{th}, 7^{th}, 10^{th} day, 3^{rd} month and 6^{th} month after the surgery, the situation of scalp wound healing was reviewed.

8.2 Safety evaluation criteria

8.2.1 Primary indicators

8.2.1.1 Cellular immunity and humoral immunity inspection were performed to determine if test product has immune reaction. The indicators of cell immunity include T cells (CD3+), absolute value of T cells (CD3) and CD4+/CD8+ ratio, and indicators of humoral immunity include IgA, IgE, IgM, IgG, CRP, C3 and C4.

8.2.1.2 Incidence of infection: the infection was determined according to the cerebrospinal fluid examination and clinical observation. The cerebrospinal fluid

examination indicators include WBC, RBC, Glu, protein and chlorine.

8.2.1.3 Incidence of seizure

8.2.1.4 Blood test and liver and kidney function test: that if the change of each indicator in the blood test and liver and kidney function test is abnormal, and if abnormal change has clinical significance was recorded. The indicators in blood test include the number of red blood cell, hemoglobin, platelet, neutrophil, white blood cell and lymphocyte, and the indicators in liver and kidney function test include alanine aminotransferase, aspartate aminotransferase, globulin, albumin, total bilirubin, urea and creatinine.

9 Clinical trial results

9.1 Trial completion time

The 1st subject (No.001) was enrolled on Jun 27, 2011 at Center 01 Zhujiang Hospital, and the last subject (No.132) was enrolled on Jun 6, 2012 at Center 03 People's Hospital of Wuhan University.

9.2 Baseline data analysis

There were 30 male patients (45.5%) and 36 female patients (54.5%) in experiment group, and 30 male patients (46.2%) and 35 female patients (53.8%) in control group, with gender equilibration between the two groups (χ^2=0.006, P=0.936). The mean age was 45.06 years in experiment group, and 45.31 years in control group, also with age equilibration between the two groups (t=0.113, P=0.910); all the patients were from Han nationality; other indicators in general information (allergy, occupation) were balanced between the two groups (P=0.563 ~ P=0.803).

All the indicators in physical examination and inspection of symptoms and signs (nausea, vomiting, meningeal irritation, height, weight, body temperature, pulse, respiration, systolic blood pressure, diastolic blood pressure) were balanced between the two groups before the surgery (P= 0.307~P=0.962).

9.3 Efficacy evaluation

Efficacy evaluation indicators included primary evaluation indicators and secondary evaluation indicators. The former was cerebrospinal fluid non-leakage rate, i.e. 10±2 days after the surgery, CT and clinical inspection were performed to confirm the presence of cerebrospinal fluid leakage and subcutaneous effusion. The latter was the situation of scalp wound healing after the surgery. The variation of following indicators was indicated with standard deviation.

9.3.1 Primary efficacy indicators

9.3.1.1 Comparison between the groups and in the group for the incidence of

cerebrospinal fluid leakage and/or subcutaneous effusion

Postoperative cerebrospinal fluid leakage and/or subcutaneous effusion in both groups were dichotomy indicators, so Pearson χ^2 test was performed. The calculation for the confidence interval of rate difference was performed using normal approximation method and precise method. The rate of no cerebrospinal fluid leakage and/or subcutaneous effusion was 93.9% (62/66) for experiment group and 92.3% (60/65) for control group. No significant difference was observed between the two groups (P=0.712), and no significant difference was observed after adjustment by the center as well (P=0.697). 95% confidence interval for the rate difference between the two groups calculated by approximation method was -7.04%~10.30%, and by precise method was -8.51%~11.96%. The non-inferiority boundary value δ defined in this trial defined was 12%. According to 95% CI calculated here, both lower limits were higher than -12%.

Combined with the results of MITT analysis, it can be inferred that the rate of no cerebrospinal fluid leakage and/or subcutaneous effusion of experiment group was non-inferior to that of control group.

9.3.1.1.1 Comparison between the groups and in the group for postoperative cerebrospinal fluid leakage

Postoperative cerebrospinal fluid leakage in both groups was dichotomy indicator, so Pearson χ^2 test was performed. The calculation for the confidence interval of rate difference was performed using normal approximation method and precise method. The rate of no cerebrospinal fluid leakage was 100% (66/66) for experiment group and 98.5% (64/65) for control group. No significant difference was observed between the two groups (P=0.312), and no significant difference was observed after adjustment by the center as well (P=0.924). 95% confidence interval for the rate difference between the two groups calculated by approximation method was 0.00%~4.53%, and by precise method was -4.10%~8.28%. The non-inferiority boundary value δ defined in this trial defined was 12%. According to 95% CI calculated here, both lower limits were lower than -12%.

The results of PP set analysis were consistent with that of MITT analysis, and it can be inferred that the rate of no cerebrospinal fluid leak of experiment group was non-inferior to that of control group.

9.3.1.2 Comparison between the groups and in the group for subcutaneous effusion

Postoperative subcutaneous effusion in both groups was dichotomy indicator, so Pearson χ^2 test was performed. The calculation for the confidence interval of rate difference was performed using normal approximation method and precise method. The rate of no subcutaneous effusion was 93.9% (62/66) for experiment group and 92.3% (60/65) for control group. No significant difference was observed between the two groups (P=0.712), and no significant difference was observed after adjustment by the center as well (P=0.924). 95% confidence interval for the rate difference between the two groups calculated by approximation method was -7.04%~10.30%, and by

precise method was -8.51%~11.96%. The non-inferiority boundary value δ defined in this trial defined was 12%. According to 95% CI calculated here, both lower limits were lower than -12%.

The results of PP set analysis were consistent with that of MITT analysis, and it can be inferred that the rate of no subcutaneous effusion of experiment group was non-inferior to that of control group.

9.3.1 Secondary efficacy indicators

9.3.2.1 Comparison between the groups and in the group for body temperature

The comparison between the groups 1-10 days after the surgery: variance analysis was performed for the comparison between the groups for body temperature before and after the surgery.

After the adjustment by baseline and center, the highest and the lowest mean temperature 1-10 days after the surgery was 37.62℃and 37.16℃for experiment group and 37.51℃ and 37.11℃for control group. No statistically significant difference was observed in the comparison between groups at each visit 1-10 days after the surgery (P=0.320~P=0.975). Except the 3rd and 10th day after the surgery (P=0.071~P=0.220), statistically significant difference in center body temperature was observed at other visits (P=0.001~P=0.046). There was o interaction effect in each group at each visit (P=0.440 ~ P = 0.973). Therefore, it could be concluded from existing results that no difference of body temperature between the groups was observed.

The results of analysis on PP population were consistent with that of MITT population.

Paired t test was used for the comparison in the group between the body temperature values at each time point after the surgery and before the surgery.The body temperature values1-10 days after the surgery of each group were all higher than preoperative ones, with statistically significant differences (P<0.001 for all).The results of analysis on PP population were consistent with that of MITT population.

9.3.2.2 Comparison between the groups and in the group for the situation of scalp wound healing

In the comparison between groups of each time point after the surgery, rank test of two independent samples was used for the comparison between groups for the situation of scalp wound healing after the surgery. Except 1 case of grade B healing in control group 10 days after the surgery, the healing of the two groups at other visits were all grade A healing. No significant difference was observed in the comparison between groups 10 days after the surgery (χ^2=1.025, P=0.311).

The results of analysis on PP population were consistent with that of MITT population. It was concluded that there was no difference of scalp wound healing between the two groups.

9.4 Safety analysis

9.4.1 Safety evaluation of laboratory indicators

No statistical difference was observed in the comparison between grups for the incidence of nausea, vomiting meningeal irritation and incidence of seizure at each time point (P=0.205~P=0.971). 10 days after the surgery, 13 patients in experiment group had 28 laboratory indicators changed from normal to abnormal with clinical significance, and 18 patients in control group had 39 laboratory indicators changed from normal to abnormal with clinical significance.

10 Clinical trial result analysis

Dura defect may be caused by brain trauma, brain tumor, cerebrovascular disease, increase of cranial content volume, congenital diseases and surgical procedure itself, and dural defect repair materials are needed for restore the dural integrity, protect the brain tissue and prevent cerebrospinal fluid leakage, intracranial infection, brain swelling, seizures and other complications. Therefore the selection of suitable and effective alternative materials to restore the integrity of the dura anatomy has important clinical significance.

Recently the materials used to repair dura mainly include autologous fascia, allograft materials, dissimilar materials, natural and synthetic materials. Although there is no tissue compatibility issue, autologous fascia has limited source, easily leads to secondary damage and has poorer strength than dura. The allograft materials easily cause virus infection and rejection reaction, etc. Heterogeneous biofilm has a risk of transmission of animal diseases. Due to the limitations of existing products, the concern about the development of new products is increasing at home and abroad.

Regenerative Dural Repair Patch developed by Medprin Regenerative Medical Technologies Co., Ltd. uses polylactic acid as the raw material with application of the principles of regenerative medicine. It has been confirmed by preliminary basic studies that dura patch has similar three-dimensional structure, which is in favor to the migration and grwth of nascent cells, promotes the repair and reconstruction of the nascent meninx, and as the material gradually degraded and absorbed by the body, nascent meningeal tissue will be gradually formed. The polymer absorbable materials with medical polylactic acid as the raw material have been widely used in the abdominal, thoracic surgery. Now according to the provision of registration regulations, Regenerative Dural Repair Patch used in the dura repair surgery must be performed the clinical validation.

Dural repair patch (Ethisorb) of USA Johnson & Johnson production is produced by absorbable polymer composite materials of polyglycolic acid (PGA), L-lactic acid and ε-caprolactone copolymer. It has three-layer sandwich type composite structure, with a middle layer of polyglycolic acid nonwoven fabric and lateral layer of L-lactic acid and ε-caprolactone copolymer film. Dural repair patch has been widely used clinically, and the safety and reliability has been demonstrated. The product of Medprin

Regenerative Medical Technologies Co., Ltd. belongs to synthetic materials as dural repair patch; therefore Ethisorb Dura Patch of Johnson & Johnson was used as control product to evaluate the safety and efficacy of Regenerative Dural Repair Patch of Medprin Regenerative Medical Technologies Co., Ltd.

A randomized, single-blind, positive control method was used to conduct non-inferiority clinical trial. The statistical results showed no significant difference in both dropout rate and exclusion rate between experiment group and control group; the difference of concomitant diseases compared with implant-combined group was not statistically significant. Sexual, age and other indicators (such as allergy, occupation, nausea, vomiting, meningeal irritation, height, weight, body temperature, pulse, respiration, systolic blood pressure and diastolic blood pressure) were balanced between the two groups. No significant difference was observed in the sites and sizes of dural defect between groups; during repair process there was no significant difference in the comparison between groups; no significant difference was observed in the situation of incision and fitting of dural patch with the dural between groups. These results suggest that the cases in these two groups are comparable, and the data can be used for the comparison of the safety and efficacy between the 2 types of materials.

The dura is an important barrier of the brain (spinal cord) from outside world, and the dura reconstruction is one of the basic procedures in neurosurgery which directly affects the postoperative recovery process and is on of the important measures to prevent postoperative cerebrospinal fluid leakage [11].

Therefore, the efficacy evaluation is performed in this trial with cerebrospinal fluid non-leakage rate as the primary efficacy indicator and the postoperative body temperature and scalp wound healing as secondary efficacy indicator. Cerebrospinal fluid leakage includes the leakage outside and under the scalp, and subcutaneous cerebrospinal fluid leakage is difficult to completely distinguished from subcutaneous bleeding or exudate, therefore the comparison was performed on cerebrospinal fluid leakage and/or subcutaneous hydrops as one indicator in the evaluation of cerebrospinal fluid non-leakage rate. The postoperative cerebrospinal fluid non-leakage and/or subcutaneous hydrops rate was 93.9% (62/66) for experiment group and 92.3% (60/65) for control group, with no significant difference between the two groups. The postoperative cerebrospinal fluid non-leakage rate was 100% (66/66) for experiment group and 98.5% (64/65) for control group, with no significant difference between the two groups. The postoperative subcutaneous hydrops rate was 93.9% (62/66) for experiment group and 92.3% (60/65) for control group, with no significant difference between the two groups. No difference was observed in the body temperature before and after the surgery at each visit between the two groups, 10 days after the surgery no statistical difference in scalp wound healing between the two groups, suggesting that there was no difference in the situation of scalp wound healing after the surgery between experiment group and control group. It can be concluded that the Regenerative Dural Repair Patch used in this trial is effective in the repair surgery of dura defect.

As external implant material the Regenerative Dural Repair Patch is also likely to lead to infection and induce seizure. In this trial, no statistical difference was observed in the incidence of nausea, vomiting, meningeal irritation and the seizure at each time point after the surgery between the two groups. 9 patients required reoperation due to the illness. There was only 1 case of mild adhesions of patch with the brain and skull, and the rest had no adhesion.10 days after the surgery, 13 patients in experiment group had 28 laboratory indicators changed from normal to abnormal with clinical significance, and 18 patients in control group had 39 laboratory indicators changed from normal to abnormal with clinical significance. No difference was observed between the two groups. Rigorous evaluation was performed for all the patients with adverse events by medical professionals, which confirmed that the adverse events occurred due to the disease itself or were caused by the surgery independent of the material used in experiment group or control group. Control product is widely used clinically with good safety, thus it can be concluded that the test product has same safety with the control product.

In summary, the nature dura patch used in this trial is a safe and effective dura repair material which is worthy of clinical use.

11 Indications, contraindications and precautions

11.1 Indications

Apply to the repair or replacement of dura defect.

11.2 Contraindications

It cannot be used in cardiovascular repair.

11.3 Warning and precautions

This product is a sterile, single-use product, but not re-sterilize and use.

Check the packaging carefully before using the product. Do not use if the original packaging is found to be damaged. Once the original packing is opened, please use immediately.

Tear or cut the packaging along a small mouth, remove the inner packaging by sterile procedure. Sterile inner package can be directly placed in a sterile environment.

This product will be fixed by the usual surgical suture. During the suture, pinhole should be 2-3mm from the patch edge.

This product can be cropped according to the clinical need, and the remaining material should be disposed as medical waste.

This product can be used even after folding.

WARNING: it should be used with caution for the site without effective control of

severe infection.

12 References

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Signatures

Name of clinical trial: Clinical trial of Regenerative Dural Repair Patch

Filing No. of clinical trial protocol: 2011MP02

Filing No. of clinical trial report: 2013MP01

I have reviewed this report, confirming that the report has described the trial process and clinical outcomes accurately and truthfully.

Leading clinical trial institution:

01 ZhuJiang Hospital of Southern Medical University

Principal investigator signature:_____ 4 M 27 D, 2013 Y

Participating clinical trial institutions:

02 Wuhan General Hospital of Guangzhou Military

Principal investigator signature:_____ 4 M 25 D, 2013 Y

03 Renmin Hospital of Wuhan University

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(Note: This page is modified from the original for the sake of translation.)