A Multi-center, Randomized, Single-blind Clinical Trial of a Novel Regenerative Synthetic Absorbable Dural Repair Patch

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ABSTRACT

Background: 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.

Objective: In this research, the efficacy and safety performance of a new developed dural substitute ReDura would be validated through a multi-center, randomized, single-blind clinical trial.

Methods: In this clinical trial, 132 subjects (66 cases for ReDura and control group respectively) would be enrolled and 6 months were followed up. The efficacy evaluation would be performed by cerebrospinal fluid non-leakage rate, body temperature observation and scalp wound healing. The safty performancewould be evaluated by such indicators as cellular immunity and humoral immunity inspection, incidence of infection, incidence of seizure.

Results: 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. 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. It can be concluded that ReDura is effective in the repair surgery. 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. 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. Safety performance was also proved in clinical.

Conclusions: This multi-center, randomized, single-blind clinical trial proved that ReDura is not inferior in efficacy and with no significant statistical difference in safety from commercially available Ethisorb. This new regenerative dural patch is worth being recommended in dural defect surgery.

Key words: Dual substitute, Dura mater, ReDura, PLLA, CSF

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.

ReDura, a recently developed and CE-approved product by Medprin Co. Ltd., is made of biodegradable Poly-L-Lactide (PLLA) and fabricated by an emerging electrospinning technology. This product adopts absorbable polymer material widely used clinically with a high

degree of three-dimensional biomimetic structure (Figure 1), 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. PLLA has been widely used in the field of medicine [3] [4], and its safety has been proven clinically [5] [6].

In this research, to further confirm the safety and efficacy, we reported the 6-month result of a multi-center, randomized, single-blind, positive parallel control, noninferiority validation clinical trial of ReDura compared with a commercially available dura mater patch (trade name: Ethisorb), which was also composed by PLLA and have not shown evident adverse clinical effect [5] [6] .

MATERIALS AND METHODS

Device Description

ReDura, provided by Medprin Biotech GmbH (Germany) is composed of absorbable materials PLLA manufactured by electrospinning technology. The control group devices Ethisorb are from Johnson & Johnson (USA) and have similar action mechanism and indications with ReDura.

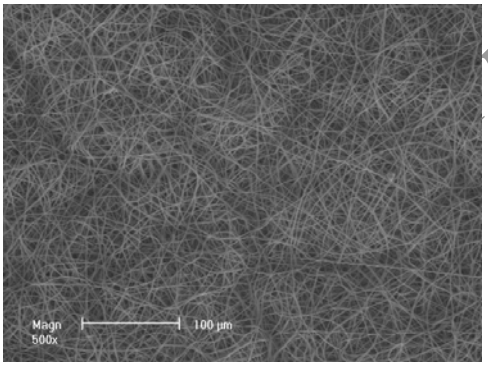

Figure 1. Micro-structure observation of ReDura patch

Study Design and Patient Population

This trial is a multi-center, randomized, single-blind, positive parallel control, noninferiority validation clinical trial, and is to provide proofs for safety and efficacy of the ReDura. Six months follow-up would be performed and results would be recorded. This clinical trial had been approved by Chinese State Food Drug Administration (CFDA) and the medical ethics committee of each hospital.

This 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 analysis of 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.

Inclusion and Exclusion Criteria

The patients who need to implement the neurosurgery repair surgery were in neurosurgery department with dura defect. Corresponding preoperative inclusion and exclusion criteria was shown in the table 1. However, during the test, the patients who applied to the items listed in Table 2 would also be excluded in the final statistical evaluation.

Table 1, Preoperative inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Age of 18-65 years, male or female.	The patients with unstable vital signs.
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	The patients with disease of heart, liver, kidney, blood system or other vital organs.

need repair surgery.	
Included patients had no obvious signs of infection before the surgery.	Pregnant or lactating women.
Included patients had no history of severe allergy and serious immunodeficiency	---
The patient and/or the guardian agreed to participate in the trial, and signed the informed consent.	---

Table 2, Intraoperative exclusion criteria

Exclusion Criteria
The patients who met exclusion criteria during the test.
Patient information missed or partially missed.
Other similar materials were used on the surgical site at the same time, or infection was developed due to other dissimilar implants.
Poor compliance.

Postoperative Outcome Measurements

The efficacy evaluation would be performed by one primary indicator (cerebrospinal fluid (CSF) non-leakage rate) to confirm the presence of cerebrospinal fluid leakage and subcutaneous effusion, and two secondary indicators (body temperature observation and scalp wound healing). The observation time points after surgery and applied methods have listed in the Table 3. For the body temperature observation, the subjects were detected for the change of body temperature, and the highest temperature of the day was recorded.

The safty performance (Table 4) would be evaluated by such indicators as cellular immunity and humoral immunity inspection to determine if test product has immune reaction, incidence of infection, incidence of seizure, routine blood test and function test on liver and kidney.

Table 3, Efficacy Evaluation Indicators

	Primary Indicator	**Secondary indicators**	
	CSF non-leakage rate [a]	**Body temperature observation**	**Scalp wound healing situation**
Observation time-point	10th day	1st, 3rd, 5th, 7th, 10th day & 3rd, 6th month	1st, 3rd, 5th, 7th, 10th day & 6th month
Methods	CT & clinical observation	Common test	Clinical observation

[a] This CSF leakage contains the occuence of cerebrospinal fluid leakage and/or subcutaneous effusion.

Table 4, Safty Evaluation indicators

Secondary complications	**N and V**	**Meningeal irritation sign**	**Seizure**	**Cellular & humoral immunity**
Observation time-point	1st, 3rd, 5th, 7th, 10th day & 3rd month			10th day
Methods	Clinical observation			Whole blood

Statistical Analysis

SAS9.2 and IBM SPSS19 a s statistical software were used for the analysis. The 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. Descriptive analysis and deductive analysis were performed on baseline data (including demographic indicators, etc.). The center effect was assessed by quantitative indicators with general

linear model and qualitative indicators with Logistic regression. The subgroup analysis was not excluded for influencing factors possibly affecting the outcome variables.

RESULTS

Patient Population

Totally 132 cases were enrolled in this trial with 66 cases for ReDura group and control group, respectively, from June 2011 to June 2012 at four hospitals across China. Detail follow-up information at different postoperative time points was compiled in the Table 5. 131 cases were included in safety evaluation population, with 66 cases in experiment group and 65 cases in control group. Finally, 117 cases were included with 57 cases in ReDura group and 60 cases in control group.

Table 5, Included cases and follow-up insituations

Follow-up	**ReDura (Target 66 cases)**	**Control (Target 66 cases)**
Surgery performed	66 cases	65 cases
1st day, postoperative	66 cases	65 cases
3rd day, postoperative	66 cases	65 cases
5th day, postoperative	65 cases	65 cases
7th day, postoperative	65 cases	64 cases
10th day, postoperative	63 cases	64 cases
3rd month, postoperative	57 cases	64 cases
6th month, postoperative	57 cases	61 cases
Final included	**57 cases (9 cases excluded)**	**60 cases (5 cases exclude and 1 case lost primary indicator information)**

Patient Demographics

The patient demographics were presented in the Table 6 and the baseline data analysis was performed.

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 ~ 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 ~ 0.962).

Table 6, Patient Demographics [a]

Item	**Description**	**ReDura**	**Control**	**Sum**	**Test statistics**	***P* Value**
Sex, No.	Male	30(45.5%)	30(46.2%)	60(45.8%)	0.006	0.936
	Femail	36(54.5%)	35(53.8%)	71(54.2%)		
Occupation, No.	Nonmanual workers	18(27.3%)	19(29.2%)	37(28.2%)	0.062	0.803
	Manual workers	48(72.7%)	46(70.8%)	94(71.8%)		.
Allergic history, No.	No	59(89.4%)	60(92.3%)	119(90.8%)	0.334	0.563

Item	Description	ReDura	Control	Sum	Test statistics	*P* Value
	Yes	7(10.6%)	5(7.7%)	12(9.2%)		.
N and V, No.	No	51(77.3%)	50(76.9%)	101(77.1%)	0.002	0.962
	Yes	15(22.7%)	15(23.1%)	30(22.9%)		.
Meningeal irritation sign, No.	Positive	7(10.6%)	4(6.2%)	11(8.4%)	0.844	0.358
	Negetive	59(89.4%)	61(93.8%)	120(91.6%)		.
Age	$\bar{x} \pm s$	45.06±12.41	45.31±12.67		0.113	0.910
	Min～Max	19.05～64.99	19.87～65.20			.
	P25～P75	37.39～56.31	35.36～56.21			.
	Median	45.41	44.50			.
Height (cm)	$\bar{x} \pm s$	163.50±8.04	164.13±7.82		0.449	0.654
	Min～Max	147.00～182.00	150.00～180.00			.
	P25～P75	158.00～170.00	158.50～171.00			.
	Median	162.50	163.00			.
Weight (kg)	$\bar{x} \pm s$	62.13±10.58	61.10±8.76		0.608	0.544
	Min～Max	40.00～86.00	46.00～82.00			.
	P25～P75	54.75～70.13	54.50～68.00			.
	Median	60.00	60.00			.
Body temperature (°C)	$\bar{x} \pm s$	36.71±0.32	36.65±0.34		1.025	0.307
	Min～Max	36.00～37.70	35.20～37.40			.
	P25～P75	36.50～36.90	36.50～36.80			.
	Median	36.70	36.70			.
Sphygmus (rate per min)	$\bar{x} \pm s$	78.80±7.67	78.68±7.27		0.097	0.923
	Min～Max	60.00～109.00	52.00～98.00			.
	P25～P75	75.00～82.00	76.00～82.50			.
	Median	80.00	80.00			.
Breath (rate per min)	$\bar{x} \pm s$	18.74±2.11	18.61±1.47		0.418	0.677
	Min～Max	14.00～26.00	16.00～22.00			.
	P25～P75	18.00～20.00	18.00～20.00			.
	Median	18.00	18.00			.
Systolic pressure (mmHg)	$\bar{x} \pm s$	127.62±19.36	126.75±15.38		0.284	0.777
	Min～Max	95.00～180.00	96.00～170.00			.
	P25～P75	114.75～140.00	116.00～137.50			.
	Median	123.50	124.00			.
Diastolic pressure (mmHg)	$\bar{x} \pm s$	80.56±14.45	78.95±9.01		0.765	0.446
	Min～Max	57.00～145.00	59.00～98.00			.
	P25～P75	70.75～85.25	70.00～84.50			.
	Median	80.00	80.00			.

[a] Pearson χ^2 test was used for such indicators as sex, occupation, N and V, meningeal irritation sign and allergic history, t-test for other indicators.

Intraoperative Analysis

The intraoperative process situation was recorded and summarized in Table 7. Except one patient quitted to perform the operation, other sugeries were successfully completed. The type of general anesthesia was applied. Most defects were located at supratentorial convexity, totally 98 cases with 50 ReDura cases (75.8% in ReDura group) and 48 control cases (73.8% in control group), others located at subtentorial convexity (18 cases), basis cranii (15 cases) and vertebral canal (2 cases). Between the two groups, no statistical significant difference was presented on defect site and defect size (P=0.137 ~ 0.991). On the incision types, the class-I was occupied over 98.5% for each group, only one (1) case in each group class-II and zero (0) case class-III occurred. During operation process, only one (1) ReDura patch applied difficult, 3 three patches comparatively smooth, other patches were successfully and smoothly used and there was significance statistical difference between the two groups. ReDura patch also had good onlay performance, only one (1) patch case not well-onlaied. No significant statistical difference was found between ReDura and control group (P=0.315).

Table 7, Intraoperative Data [a]

Item		Descrip.	ReDura	Control	Sum	Test statistics	*P* Value
Defect site, No.	Supratentorial convexity	No	16(24.2%)	17(26.2%)	33(25.2%)	0.063	0.801
		Yes	50(75.8%)	48(73.8%)	98(74.8%)		.
	Subtentorial convexity	No	54(81.8%)	59(90.8%)	113(86.3%)	2.214	0.137
		Yes	12(18.2%)	6(9.2%)	18(13.7%)		.
	Basis cranii	No	61(92.4%)	55(84.6%)	116(88.5%)	1.969	0.161
		Yes	5(7.6%)	10(15.4%)	15(11.5%)		.
	vertebral canal	No	65(98.5%)	64(98.5%)	129(98.5%)	0.000	0.991
		Yes	1(1.5%)	1(1.5%)	2(1.5%)		.
Defect size [b]	Major diameter (cm)	$\bar{x} \pm s$	4.74±4.71	4.04±2.09		1.105	0.272
		Min～Max	1.00～40.00	0.40～12.00			.
		P25～P75	3.00～5.00	3.00～5.00			.
		Median	4.00	4.00			.
	Minor diameter (cm)	$\bar{x} \pm s$	3.99±5.97	3.71±2.36		0.354	0.724
		Min～Max	0.50～50.00	0.30～12.00			.
		P25～P75	2.00～4.00	2.00～4.75			.
		Median	3.00	3.20			.
Incision, No.		Class-I	65(98.5%)	64(98.5%)	129(98.5%)	0.000	0.991
		Class-II	1(1.5%)	1(1.5%)	2(1.5%)		.
		Class-III	0(0.0%)	0(0.0%)	0(0.0%)		
Patch application process [b], No.		Smooth	62(93.9%)	65(100.0%)	127(96.9%)	2.002	0.045*
		Comparatively smooth	3(4.5%)	0(0.0%)	3(2.3%)		
		Different	1(1.5%)	0(0.0%)	1(0.8%)		.
		A little different	0(0.0%)	0(0.0%)	0(0.0%)		.
Onlay, No.		No	1(1.5%)	0(0.0%)	1(0.8%)	1.008	0.315
		Yes	64(98.5%)	65(100.0%)	129(99.2%)		.

[a] Rand test used on patch application process was from randed data. Pearson χ^2 test was used on qualitative indicators, t-test on quatitative indicators.

Absence of CSF leak

Comparison results between the groups for the incidence of cerebrospinal fluid leakage and/or subcutaneous effusion were shown in the Table 8-1 and Table 8-2.

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 centerring 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%. 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.

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%. It can be inferred that the rate of no cerebrospinal fluid leak of experiment group was non-inferior to that of control group.

Table 8-1, Cerebrospinal fluid leakage and/or subcutaneous effusion data on 10th day *

Group	Cerebrospinal fluid leakage and/or subcutaneous effusion, No.		95% CI for rate difference	*P*1	*P*2
	No	Yes			
ReDura	62(93.9%)	4(6.1%)	-7.04～10.30 [a]	0.712	0.697
Control	60(92.3%)	5(7.7%)	-8.51～11.96 [b]	.	.

* *P*1 was the P value through Pearson χ^2 tes and P value after centering.

[a] approximation method. [e] precise method.

Table 8-2, Cerebrospinal fluid leakage data on 10th day

Group	Cerebrospinal fluid leakage, No.		95% CI for rate difference	*P*1	*P*2
	No	Yes			
ReDura	66(100.0%)	0(0.0%)	0.00~4.53[a]	0.312	0.924
Control	64(98.5%)	1(1.5%)	-4.10~8.28[e]	.	.

**P*1 was the P value through Pearson χ^2 tes and P value after centering.

[a] approximation method. [e] precise method.

Body Temperature Analysis

Body temperature data as the secondary indicator was analyzed in the Table 9.

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 bserved.

Table 9, Body temperature data [a]

ITEMS					Between-column D-value after baseline, center adjustment			P-value after baseline, center adjustment		
Time-point	Group	No.	Temp.	Temp. adjusted	Comparison	95% CI	P value	Between-column	Center	Between-column × center
1st day, postop	Control	66	37.69±0.07	37.51±0.08				.	.	.
	ReDura	65	37.57±0.07	37.62±0.07	- VS. Control	-0.32～0.10	0.3198	.	.	.
	.	.			Whole		0.3172	0.320	0.046	0.581
3rd day, postop	Control	66	37.56±0.09	37.40±0.10				.	.	.
	ReDura	64	37.47±0.08	37.47±0.10	- VS. Control	-0.34～0.21	0.6289	.	.	.
	.	.			Whole		0.5700	0.629	0.220	0.620
5th day, postop	Control	64	37.46±0.10	37.28±0.11				.	.	.
	ReDura	63	37.44±0.09	37.32±0.11	- VS. Control	-0.35～0.27	0.8031	.	.	.
	.	.			Whole		0.9061	0.803	0.006	0.973
7th day, postop	Control	63	37.33±0.10	37.18±0.11				.	.	.
	ReDura	63	37.35±0.10	37.19±0.11	- VS. Control	-0.32～0.31	0.9746	.	.	.
	.	.			Whole		0.7677	0.975	0.001	0.795
10th day, postop	Control	62	37.19±0.08	37.11±0.10				.	.	.
	ReDura	62	37.23±0.09	37.16±0.10	- VS. Control	-0.33～0.22	0.6915	.	.	.
	.	.			Whole		0.6473	0.692	0.071	0.440
3th month, postop	Control	20	36.96±0.08	37.02±0.10				.	.	.
	ReDura	19	36.93±0.11	36.99±0.08	- VS. Control	-0.23～0.29	0.8256	.	.	.
	.	.			Whole		0.7865	0.826	0.013	0.725
6th month, postop	Control	6	36.78±0.13	36.89±0.09				.	.	.
	ReDura	12	36.90±0.08					.	.	.
	.	.			Whole		0.5286	0.864	0.244	0.626

[a] The means was adjusted by least square method. postop, postoperatively; Temp., temperature.

Scap Wound Healing Performance

In the comparison between groups of each time point after the surgery in the Table 10, 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 second grade intention in control group 10 days after the surgery, the

healings of the two groups at other visits were all first grade intention. No significant difference was observed in the comparison between groups 10 days after the surgery (χ^2=1.025, P=0.311). It was concluded that there was no difference of scalp wound healing between the two groups.

Table 10, Scap wound healing situation data

Observation time-point	Group	Incision healing type			Sum.	χ^2	*P* Value
		First grade intention	Second grade intention	Third grade intention			
1st day, postop	Control	65(100.0%)	0(0.0%)	0(0.0%)	65(100.0%)		.
	ReDura	66(100.0%)	0(0.0%)	0(0.0%)	66(100.0%)		.
3rd day, postop	Control	64(100.0%)	0(0.0%)	0(0.0%)	64(100.0%)		.
	ReDura	66(100.0%)	0(0.0%)	0(0.0%)	66(100.0%)		.
5th day, postop	Control	63(100.0%)	0(0.0%)	0(0.0%)	63(100.0%)		.
	ReDura	64(100.0%)	0(0.0%)	0(0.0%)	64(100.0%)		.
7th day, postop	Control	63(100.0%)	0(0.0%)	0(0.0%)	63(100.0%)		.
	ReDura	63(100.0%)	0(0.0%)	0(0.0%)	63(100.0%)		.
10th day, postop	Control	60(98.4%)	1(1.6%)	0(0.0%)	61(100.0%)	1.025	0.311
	ReDura	62(100.0%)	0(0.0%)	0(0.0%)	62(100.0%)		.
6th month, postop	Control	60(100.0%)	0(0.0%)	0(0.0%)	60(100.0%)		.
	ReDura	57(100.0%)	0(0.0%)	0(0.0%)	57(100.0%)		.

Safty Indicators Observation

Safety related indicators were evaluated and summarized in the Table 11-13. It can be found that 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 ~ 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.

Table 11, Secondary complications observation analysis

Indicators	Time-point	Group	If with related complications		Sum	χ^2	P Value
			No	Yes			
N and V	1st day	Control	54(83.1%)	11(16.9%)	65(100.0%)	0.390	0.532
		ReDura	52(78.8%)	14(21.2%)	66(100.0%)		.
	3rd day	Control	57(89.1%)	7(10.9%)	64(100.0%)	0.508	0.476
		ReDura	56(84.8%)	10(15.2%)	66(100.0%)		.
	5th day	Control	60(95.2%)	3(4.8%)	63(100.0%)	0.135	0.713
		ReDura	60(93.8%)	4(6.3%)	64(100.0%)		.
	7th day	Control	60(96.8%)	2(3.2%)	62(100.0%)	0.358	0.550
		ReDura	62(98.4%)	1(1.6%)	63(100.0%)		.
	10th day	Control	59(96.7%)	2(3.3%)	61(100.0%)	0.667	0.414
		ReDura	58(93.5%)	4(6.5%)	62(100.0%)		.
	6th month	Control	59(98.3%)	1(1.7%)	60(100.0%)	0.397	0.529

Indicators	Time-point	Group	If with related complications		Sum	χ^2	P Value
			No	Yes			
		ReDura	55(96.5%)	2(3.5%)	57(100.0%)		.
Meningeal irritation sign	1st day	Control	52(80.0%)	13(20.0%)	65(100.0%)	0.243	0.622
		ReDura	55(83.3%)	11(16.7%)	66(100.0%)		.
	3rd day	Control	51(79.7%)	13(20.3%)	64(100.0%)	1.610	0.205
		ReDura	58(87.9%)	8(12.1%)	66(100.0%)		.
	5th day	Control	54(85.7%)	9(14.3%)	63(100.0%)	0.087	0.768
		ReDura	56(87.5%)	8(12.5%)	64(100.0%)		.
	7th day	Control	54(87.1%)	8(12.9%)	62(100.0%)	0.095	0.758
		ReDura	56(88.9%)	7(11.1%)	63(100.0%)		.
	10th day	Control	54(88.5%)	7(11.5%)	61(100.0%)	0.105	0.746
		ReDura	56(90.3%)	6(9.7%)	62(100.0%)		.
	6th month	Control	60(100.0%)	0(0.0%)	60(100.0%)		.
		ReDura	57(100.0%)	0(0.0%)	57(100.0%)		.
Seizure	1st day	Control	65(100.0%)	0(0.0%)	65(100.0%)		.
		ReDura	66(100.0%)	0(0.0%)	66(100.0%)		.
	3rd day	Control	63(98.4%)	1(1.6%)	64(100.0%)	1.039	0.308
		ReDura	66(100.0%)	0(0.0%)	66(100.0%)		.
	5th day	Control	63(100.0%)	0(0.0%)	63(100.0%)		.
		ReDura	64(100.0%)	0(0.0%)	64(100.0%)		.
	7th day	Control	62(100.0%)	0(0.0%)	62(100.0%)		.
		ReDura	63(100.0%)	0(0.0%)	63(100.0%)		.
	10th day	Control	60(98.4%)	1(1.6%)	61(100.0%)	1.025	0.311
		ReDura	62(100.0%)	0(0.0%)	62(100.0%)		.
	6th month	Control	59(98.3%)	1(1.7%)	60(100.0%)	0.001	0.971
		ReDura	56(98.2%)	1(1.8%)	57(100.0%)		.

Table 12, Preoperative normal laboratory indicators changed to abnormal with clinical significance on the 10th day postoperatively

Research Center	Subject #	Group	Sex	Indicators	Preop.	Decision value preoper.	10th day, postop.	Decision value at 3rd follow-up
01	1	Control	Female	hemoglobin	112	1	100	3
				blood platelet	161	1	377	3
				white blood cell counting	4.3	1	13.9	3
01	5	Control	Female	white blood cell counting	7.8	1	11.9	3
01	8	Control	Male	white blood cell counting	9.6	1	11.2	3
				CRP	1.02	1	27.1	3
01	10	Control	Male	Neutrophils	65.4	1	85.8	3
				white blood cell counting	6.7	1	28.8	3
				leukomonocyte	20.9	1	5.4	3

Research Center	Subject #	Group	Sex	Indicators	Preop.	Decision value preoper.	10th day, postop.	Decision value at 3rd follow-up
				CRP	1.22	1	14.7	3
01	15	ReDura	Female	hemoglobin	128	1	100	3
				Neutrophils	63	1	71.3	3
01	16	Control	Male	hemoglobin	158	1	128	3
				Neutrophils	60.5	1	78.9	3
				blood platelet	276	1	427	3
				white blood cell counting	8.16	1	15	3
				leukomonocyte	23.5	1	10.8	3
01	21	Control	Female	red blood cell counting	4.55	1	3.4	3
				hemoglobin	131	1	103	3
01	25	Control	Female	white blood cell counting	5.3	1	15	3
01	27	ReDura	Male	red blood cell counting	4.06	1	3.32	3
				$CD4^+/CD8^+$ ratio	1.55	1	3.41	3
01	34	Control	Male	CRP	0.38	1	19.2	3
01	40	ReDura	Female	white blood cell counting	7.75	1	17.7	3
01	41	Control	Male	red blood cell counting	3.93	1	3.09	3
				hemoglobin	134	1	96.8	3
				Neutrophils	57.8	1	81.4	3
				white blood cell counting	7.6	1	17.2	3
				leukomonocyte	25	1	11.1	3
01	42	Control	Male	white blood cell counting	9.2	1	11.78	3
				CRP	0.33	1	19.1	3
01	44	Control	Male	white blood cell counting	5.8	1	11.2	3
				CRP	0.24	1	32.5	3
01	54	Control	Female	CRP	0.54	1	19.1	3
01	55	ReDura	Female	Neutrophils	50.9	1	84.5	3
				white blood cell counting	7.98	1	19.2	3
				albumin	39.6	1	34.2	3
				Urea units	3.8	1	11.4	3
01	57	ReDura	Female	hemoglobin	119	1	88.8	3
				Neutrophils	54.9	1	82.1	3
				blood platelet	282	1	389	3
				white blood cell counting	5.24	1	12.7	3
				CRP	1.02	1	47.4	3
01	59	Control	Male	white blood cell counting	5.27	1	20	3
				Alanine aminotransferase	20	1	275	3
				CRP	0.14	1	22.4	3
01	60	ReDura	Female	red blood cell counting	4.17	1	3.15	3
				hemoglobin	125	1	91	3

Research Center	Subject #	Group	Sex	Indicators	Preop.	Decision value preoper.	10th day, postop.	Decision value at 3rd follow-up
				Neutrophils	61.9	1	75.6	3
				white blood cell counting	6.4	1	10.6	3
				CRP	1.43	1	33.9	3
02	65	ReDura	Female	red blood cell counting	4.44	1	2.61	3
				hemoglobin	127	1	74	3
03	108	ReDura	Female	T cells ($CD3^+$)	79.3	1	17.7	3
03	109	Control	Female	Alanine aminotransferase	31	1	110	3
				Aspartate aminotransferase	22	1	54	3
03	113	ReDura	Male	white blood cell counting	9.72	1	16.81	3
03	115	Control	Female	CRP	5	1	40.45	3
03	117	Control	Female	white blood cell counting	5.71	1	17.59	3
03	118	ReDura	Female	CRP	5	1	26.61	3
03	119	Control	Female	Aspartate aminotransferase	19	1	110	3
04	77	ReDura	Female	white blood cell counting	6.99	1	14.81	3
04	79	ReDura	Female	hemoglobin	141	1	111	3
04	91	Control	Female	hemoglobin	144	1	86	3
				blood platelet	179	1	51	3

Table 13, Preoperative abnormal laboratory indicators without clinical significance changed to with clinical significance on the 10th day postoperatively

Research center	Subjects #	Group	Sex	Indicators	Preop.	Decision value preoper.	10th day, postop.	Decision value at 3rd follow-up
01	8	Control	Male	Neutrophils	78	2	77.7	3
01	10	Control	Male	IgE	199	2	244	3
01	30	Control	Female	white blood cell counting	11.8	2	18.3	3
01	40	ReDura	Female	blood platelet	443	2	433	3
01	59	ReDura	Male	Neutrophils	47	2	83.7	3
03	97	ReDura	Male	T celles ($CD3^+$)	58.9	2	46.7	3
03	108	ReDura	Female	$CD4^+/CD8^+$ ratio	2.11	2	2.63	3
03	118	ReDura	Female	T celles ($CD3^+$)	55.9	2	38.4	3
				$CD4^+/CD8^+$ ratio	3.08	2	2.18	3
04	77	ReDura	Female	Neutrophils	76.91	2	92.01	3
				T celles ($CD3^+$)	32	2	53	3
				T cells absolute value	316.8	2	265	3
04	91	Control	Female	red blood cell counting	5.21	2	3.04	3
				Neutrophils	90.7	2	94.2	3
				white blood cell counting	27.75	2	24.67	3

Adverse Cases Analysis

The adverse cases were also recorded and analyzed when some medical indences happened, no matter it was due to medical device or not. It would be categorized as serious adverse cases if such sevious events happened as patient dying, getting health serious worsen or fatal or permanent hurt, or delaying the time in hospital, and so on. Other events could be defined as general adverse cases.

The adverse cases data was analyzed and summarized in the Table 14 (general adverse cases data) and Table 15 (serious adverse cases data). Pearson χ^2 test was used for comparing of the two groups. The ReDura group occupied 42.4% general adverse cases while 53.8% for the control group. There was no significant statistical significance (χ^2=1.711, P=0.191) between the two groups, same statistical results concluded on groups serious adverse cases (χ^2=0.070, P=0.791), ReDura 18.2% versus control 20.0%.

Table 14, General adverse cases comparison between groups

Group	If with general adverse cases		Sum	χ^2	P
	No, No.	Yes, No.			
Control	30(46.2%)	35(53.8%)	65(100.0%)	1.711	0.191
ReDura	38(57.6%)	28(42.4%)	66(100.0%)		.
Sum	68(51.9%)	63(48.1%)	131(100.0%)		.

Table 15, Serious adverse cases comparison between groups

Group	If with serious adverse cases		Sum	χ^2	P
	No, No.	Yes, No.			
Control	52(80.0%)	13(20.0%)	65(100.0%)	0.070	0.791
ReDura	54(81.8%)	12(18.2%)	66(100.0%)		.
Sum	106(80.9%)	25(19.1%)	131(100.0%)		.

DISCUSSION

The ideal dural substitute should prevent CSF leaks, have similar mechanical properties, especially strength and flexibility to human dura, be nonimmunogenic, not cause potential risk of infections, and be abundantly available and easy to store [2,16]. The regenerative patch ReDura in this research, fabricated by bioabsorbable materials, owned 3D fibrious structure similar to native dura which benefits to the migration of nascent cell 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.

In this clinical trial, the statistical results showed no significant difference and were balanced between experiment group and control group in 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). 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 two 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. 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. 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. It can be concluded that the test product has same safety with the control product.

CONCLUSIONS

This trial is a multi-center, randomized, single-blind, clinical trial, and is to provide proofs for safety and efficacy of the ReDura. It can be seen from above study resulst that the ReDura is not inferior in efficacy and with no significant statistical difference in safety from commercially available Ethisorb. This new regenerative dural patch is worth being recommended in dural defect surgery and will bring benefits to worldwide patient