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*Original Article*

# Efficacy of microsurgery for congenital neural tube defects in newborns

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**Abstract:** Objective: The purpose of this study was to investigate the clinical value of microsurgery in the treatment of congenital neural tube defect (CNTD) in newborns. Methods: Eighty-five CNTD newborns withlipomyelomeningocele admitted to our hospital from March 2016 to December 2018 were retrospectively selected as study subjects. They were divided into a study group (SG, 43 cases, that received meningocele repair combined with tethered cord release within 6 h to 30 d after birth) and the control group (CG, 42 cases, that received meningocele repair combined with tethered cord release past 30 d after birth) according to the treatment regimen. Newborns in both groups were evaluated for short-term and long-term outcome of the surgery and the degree of postoperative untethering, and both groups were followed up dynamically to record changes in gross motor function and quality of life and assess risk factors. Results: In terms of short-term outcomes, the total effective rate was 93.02% in SG and 85.71% in CG ($P > 0.05$); in terms of the long-term outcomes, the total effective rate was 88.37% in SG and 69.05% in CG ($P < 0.05$). The postoperative release of the newborns was evaluated according to the Kirollos grading system, which showed that SG had 40 (93.02%) cases of grade 1 untethering, 3 (6.98%) cases of grade 2 untethering, and 0 case of grade 3 untethering, and CG had 30 (71.43%) cases of grade 1 untethering, and 12 (28.57%) cases of grade 2 untethering. At 6 months postoperatively, there were no significant differences in gross motor function and quality of life scores between the two groups ($P > 0.05$), but at 1 year, 3 years and 4 years postoperatively, the gross motor function and quality of life scores of newborns in the SG were significantly higher than those in the CG ($P < 0.05$). Multivariate logistic regression analysis showed that age > 1 month was an independent risk factor for surgical outcome ($P < 0.05$). Conclusion: Microsurgery has better short-term and long-term outcomes for newborns with CNTD, and the newborns showed an improvement in the long-term postoperative motor function and quality of life.

**Keywords:** Microsurgery, newborns, congenital neural tube defects, short-term and long-term outcomes, motor function, quality of life

## Introduction

Congenital neural tube defect (CNTD) is a serious birth malformation of the central nervous system [1], which is the formation of an exposed nervous system due to failed or incomplete closure of neural tube, usually occurring in the third and fourth week of embryonic development [2]. The main manifestations of CNTD include anencephaly, encephalocele, myelomeningocele, spina bifida/spina bifida occulta, cleft lip, and cleft palate, among which spina bifida has the highest incidence and the most diverse types of presentation [3, 4]. CNTD is a complex disease influenced by multifactorial, and genetic, and environmental factors, and data showed that there were about 260,000 neonates born with CNTD worldwide in 2015, and about 13% of children with CNTD died in the first year of life, and 18% died before the age of 18. Even children who survived with CNTD suffered from severe disabilities, which could cause a serious burden to themselves, their families, and society; therefore, medical experts generally recommend that pregnant women terminate their pregnancies after the fetus is diagnosed with neural tube abnormality and recommend early intervention for surviving newborns to improve the prognosis [5, 6].

At present, the treatment options for children with CNTD mainly include surgical treatment for

lipomyelomeningocele, cerebral bypass surgery, and spinal cord embolization release. Early clinical treatment options for CNTD are mainly sac ligation or iodine sclerosis of cystic masses, but the success rate of surgical treatment is low, and patients often die of hydrocephalus or severe infection [7, 8]. Meningocele repair mostly within 72 h after delivery thus gradually emerged, resulting in a lower rate of central nervous system infection, significantly reduced mortality, and improved neurological function [9, 10].

Neonatal spinal meningoceles grow faster after birth due to the effect of cerebrospinal fluid, and in some cases, the size of meningocele can reach 12 times of that at birth, and the increase of the masses can produce compression on the children's cones, aggravate clinical symptoms and increase the difficulty of surgery; therefore, early surgery is recommended for children with CNTD, and surgery on meningocele masses within 3 d is called ultra-early surgery. Since newborns have thinner spinal cord and cauda equina, minor misoperations can cause serious damage, so ultra-early surgery is usually performed under a microscope, which has less stimulation on children, enabling faster recovery after surgery [11]. However, ultra-early surgery can also be influenced by many factors, such as the skill level of the operator and the type of spinal nerve adhesions in children. Clinically, it is generally recommended that an incision should be made from the upper normal dura, and a sharp division should be used to release the adherent spinal nerves in CNTD children with concurrent cystic meningocele or lipoma, but attention should be paid not to damage the nerves, which is one of the key factors affecting the success or failure of the surgery.

This study was conducted to demonstrate in detail the clinical value of microsurgery in the treatment of CNTD in newborns, thereby providing a clinical reference for improving the prognosis.

## Materials and methods

### *General data*

Eighty-five CNTD newborns with lipomyelomeningocele admitted to our hospital from March 2016 to December 2018 were retrospectively selected and divided into the study group (SG, 43 cases, given meningocele repair combined with tethered cord release within 6 h to 30 d after birth) and the control group (CG, 42 cases, given meningocele repair combined with tethered cord release after 30 d of birth) according to the treatment regimen.

*Inclusion criteria:* (1) all newborns with definite clinical diagnosis of CNTD [12]; and (2) those with complete medical records. The study was approved by the Ethics Committees of Chinese PLA General Hospital (No. 2021YFA1101703).

*Exclusion criteria:* (1) children with brain tumors, epilepsy, and organic lesions; (2) children who had recently undergone surgery for cerebral palsy; (3) children with allergic constitution; (4) children who were included in other uncompleted clinical studies; and (5) children with bladder and rectal dysfunction were excluded.

### *Treatment method*

In both groups, tracheal intubation was used for general anesthesia, and a transverse or longitudinal lumbosacral incision was made to remove the local subcutaneous lesions. The surgical procedures of both groups were as follows: (1) The specific procedures to release spinal cord compression included expanding the cone plate, removing the soft tissue or bony tissue compressing the nerve, exposing the normal dura and lipoma, followed by microscopic removal of the adhesions and lipoma (or subtotal resection if it was difficult to distinguish the lipoma from the spinal cord or nerve boundary to avoid damage to the spinal cord); after removal of the lesion, the cauda equina nerve was separated under neurophysiological cooperation. The spinal cord was released from the spinal cord embolus, and tension was reduced by separating the cauda equina nerve and removing the thickened and shortened end filaments after freeing the end filaments. (2) The spinal cord was released from sources of traction. The protruding spinal cord and spinal nerves were exposed under the microscope, and the spinal nerves attached to the abnormal filament terminals were exposed, thus achieving the purpose of complete release (attention was paid to not to damage the sacral nerves on both sides of the filament terminals during this process). Spinal cord fluctuations after tethering indicated that the stretched spi-

nal cord had loosened. After successful release of the nerve, the protruding spinal cord tissue and the nerve bundle were retracted, the dura was repaired and enlarged with artificial dura, and sutures were performed (note that space should be reserved for the retracted spinal cord tissue during this procedure in order to avoid secondary adhesions). The subcutaneous tissues should be protected as much as possible after surgery, and subcutaneous latent extension or relaxing sutures could be used if necessary.

*Observation indices*

(1) The clinical efficacy was evaluated at 6 months and 4 years after surgery for both groups, and the efficacy criteria were markedly effective (normal urination and defecation function or no symptoms related to tethered cord), effective (either urination and defecation function or limb lesions was significantly improved), ineffective (no significant change in symptoms after surgery), and aggravation (worsening of symptoms or new symptoms). The total effective rate = (markedly effective + effective)/total number of cases × 100%.

(2) The release was evaluated according to the Kirollos grading method [13]. Grade 1: disappearance of all factors causing spinal cord embolism; Grade 2: partial release; Grade 3: unsuccessful release.

(3) Changes in gross motor function and quality of life of the newborns in both groups were evaluated by the Gross Motor Function Measure (GMFM) [14] and PedsQL™ Pediatric Quality of Life Inventory [15], respectively, at 6 months, 1 year, 2 years, and 4 years postoperatively. The GMFM scale consists of five dimensions, including lying and rolling, sitting, crawling and kneeling, standing, and walking, running and jumping, with a total of 88 items. Each item is scored on a 4-point Likert scale from 0 to 3, with 0 indicating that child does not initiate, 1 indicating that initiates < 10% of the task, 2 indicating that child partially completes the task (10% to < 100% of the activity), and 3 indicating that child completes the task (100%). The total score of the scale is the sum of the items, and the higher scores represent the stronger motor ability. The Pediatric Quality of Life Inventory consists of five dimensions, including physical functioning, physical symptoms, emotional functioning, social functioning, and cognitive functioning, with a total of 45 items. Each item is divided into 5 levels from 0 to 4, corresponding to a score of 100, 75, 50, 25 and 0, respectively. The total score of the scale is the sum of the scores of each item divided by the number of items, and higher scores represent higher quality of life.

(4) According to the follow-up results, univariate and multivariate logistic regression analysis were performed on the risk factors affecting the surgical outcome.

*Statistical methods*

SPSS22.0 statistical software was used to analyze the data. The measured data were described as mean ± standard deviation (SD), normal distribution and homogeneity of variance were tested, and the t-test was used for the differences between groups meeting normal distribution. The Mann-Whitney U test was used for data with non-parametric variance. The chi-square test was used for the difference of the counted data between the groups, and the difference analysis of multiple time points between the two groups was performed firstly by the analysis of variance to test whether there was any difference between the two groups, and then the post-hoc analysis was used to carry out the pairwise comparison. Logistic regression was used for multivariate regression analysis. $P < 0.05$ indicated a significant difference, and the graphing software used in this study was GraphPad Prism 8.3 [16].

## Results

*Comparison of baseline data*

There was no significant difference between the two groups in terms of baseline clinical data ($P > 0.05$) (**Table 1**).

*Short-term and long-term comparison of treatment effects*

In terms of short-term outcomes, there were 18 cases of markedly effective, 22 cases of effective, and 3 cases of ineffective in SG, with a total effective rate of 93.02%, while there were 14 cases of markedly effective, 22 cases of effective, 5 cases of ineffective, and 1 case

**Table 1.** Comparison of baseline data (mean ± SD)/[n (%)]

| General data | | Study group (n=43) | Control group (n=42) | $t/\chi^2$ | *P* |
|---|---|---|---|---|---|
| Gender | Male | 26 | 27 | 0.132 | 0.716 |
| | Female | 17 | 15 | | |
| Mean age (months) | | 0.79±0.11 | 1.34±0.18 | 17.043 | < 0.001 |
| Mean weight (kg) | | 3.01±0.39 | 2.98±0.21 | 0.44 | 0.661 |
| Type of paralysis | Hemiplegia | 13 | 13 | 0.447 | 0.780 |
| | Double paralysis | 15 | 17 | | |
| | Quadriplegia | 15 | 12 | | |

**Table 2.** Comparison of short-term outcome [n (%)]

| Group | Number of cases | Markedly effective | Effective | Ineffective | Aggravation | Effective |
|---|---|---|---|---|---|---|
| Study group | 43 | 18 | 22 | 3 | 0 | 40 (93.02) |
| Control group | 42 | 14 | 22 | 5 | 1 | 36 (85.71) |
| $\chi^2$ | - | - | - | - | - | 1.199 |
| *P* | - | - | - | - | - | 0.274 |

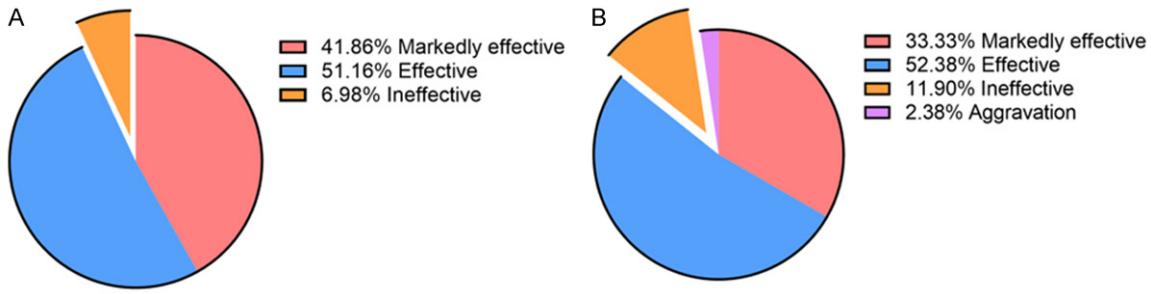


**Figure 1.** Comparison of short-term outcomes. A: Study group. B: Control group.

**Table 3.** Comparison of the long-term outcome [n (%)]

| Group | Number of cases | Markedly effective | Effective | Ineffective | Aggravation | Effective |
|---|---|---|---|---|---|---|
| Study group | 43 | 12 | 26 | 4 | 1 | 38 (88.37) |
| Control group | 42 | 9 | 20 | 9 | 4 | 29 (69.05) |
| $\chi^2$ | - | - | - | - | - | 4.753 |
| *P* | - | - | - | - | - | 0.029 |

of aggravation in CG, with a total effective rate of 85.71%, exhibiting no significant difference ($P > 0.05$) (**Table 2**; **Figure 1**). In terms of long-term follow-up, there were 12 cases of markedly effective, 26 cases of effective, 4 cases of ineffective, and 1 case of aggravation, with a total effective rate of 88.37% in SG, while there were 9 cases of markedly effective, 20 cases of effective, 9 cases of ineffective, and 4 cases of aggravation, with a total effective rate of 69.05%, exhibiting a significant difference ($P < 0.05$) (**Table 3**; **Figure 2**). The results showed that the total effective rate in both groups decreased over time, but there was no significant difference before and after treatment ($P > 0.05$) (**Figure 3**).

*Analysis of release grading*

In SG, there were 40 (93.02%) cases of grade 1, 3 (6.98%) cases of grade 2, and 0 case of grade 3; in CG, there were 30 (71.43%) cases of grade 1 and 12 (28.57%) cases of grade 2. The proportion of grade 1 in SG was significantly higher than that of the CG ($P < 0.05$) (**Table 4**).

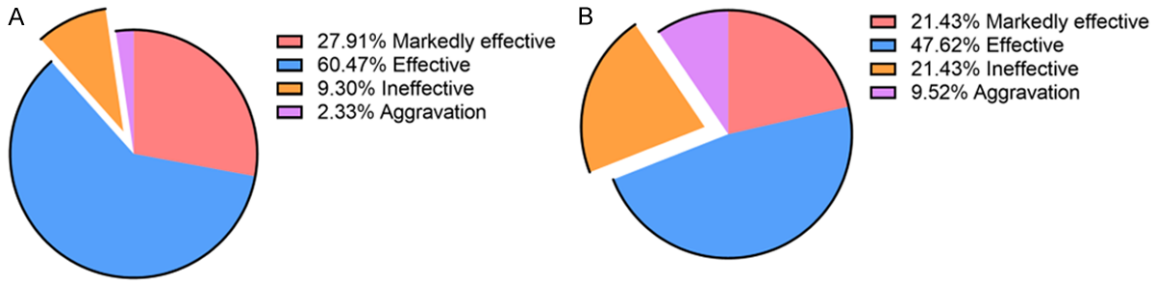


**Figure 2.** Comparison of long-term treatment effect. A: Study group. B: Control group.

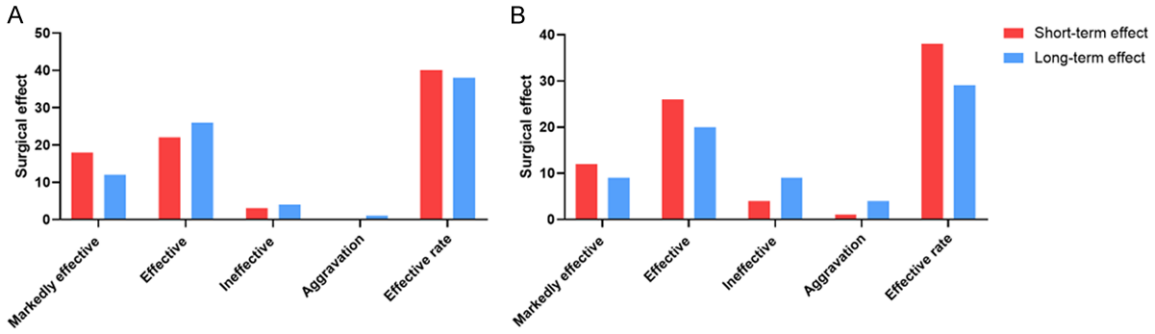


**Figure 3.** Changes in treatment effect. A: Study group. B: Control group.

**Table 4.** Analysis of release grading in the two groups

| Group | Number of cases | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|---|
| Study group | 43 | 40 | 3 | 0 |
| Control group | 42 | 30 | 12 | 0 |
| $\chi^2$ | - | 6.818 | 6.818 | - |
| *P* | - | 0.009 | 0.009 | - |

*Analysis of changes in gross motor function and quality of life*

The differences between the two groups in gross motor function and quality of life scores were not significant at 6 months postoperatively ($P > 0.05$). At 1 year, 2 years, and 4 years postoperatively, the newborns in SG had significantly higher gross motor function and quality of life scores than those in CG ($P < 0.05$) (**Tables 5**, **6** and **Figure 4**).

*Analysis of risk factors affecting surgical outcome*

Univariate analysis showed that surgical age was a risk factor influencing surgical outcome ($P < 0.05$), while other factors such as gender, mean weight, urination and defecation function, and nerve damage, were not significantly correlated with surgical outcome ($P > 0.05$) (**Table 7**). Multivariate Logistic regression analysis showed that age > 1 month was an independent risk factor for surgical outcome ($P < 0.05$) (**Table 8**).

## Discussion

CNTD, also known as neural tube closure insufficiency, is a congenital malformation that occurs during neural tube development and is manifested as neural tube closure failure [17]. The clinical manifestation of CNTD varies widely, with severe cases of craniosynostosis and anencephaly leading to miscarriage, stillbirth or death shortly after birth, and mild cases with meningocele and spondylolisthesis. Although children with meningocele or spondylolisthesis have good prognosis and long survival time after treatment, the disability rate of such children is still high, posing a public health burden [18].

Epidemiological data showed that the overall incidence of CNTD in China was about 13.95 per 10,000 in 1996, higher than other coun-

**Table 5.** Analysis of changes in gross motor function (mean ± SD)

| Group | Number of cases | 6 months postoperatively | 1 year postoperatively | 2 year postoperatively | 4 year postoperatively |
|---|---|---|---|---|---|
| Study group | 43 | 35.39±3.33 | 40.49±4.31 | 43.39±3.20 | 44.90±4.99 |
| Control group | 42 | 34.98±2.98 | 37.18±3.48 | 41.22±2.98 | 40.18±5.40 |
| *t* | - | 0.598 | 3.89 | 3.234 | 4.187 |
| *P* | - | 0.551 | < 0.001 | 0.002 | < 0.001 |

**Table 6.** Analysis of changes in the quality of life (mean ± SD)

| Group | Number of cases | 6 months postoperatively | 1 year postoperatively | 2 year postoperatively | 4 year postoperatively |
|---|---|---|---|---|---|
| Study group | 43 | 40.38±4.44 | 50.18±5.41 | 56.59±3.09 | 66.98±6.50 |
| Control group | 42 | 39.98±4.59 | 46.59±4.89 | 52.19±2.98 | 61.29±4.39 |
| *t* | - | 0.408 | 3.207 | 6.68 | 4.718 |
| *P* | - | 0.684 | 0.002 | < 0.001 | < 0.001 |

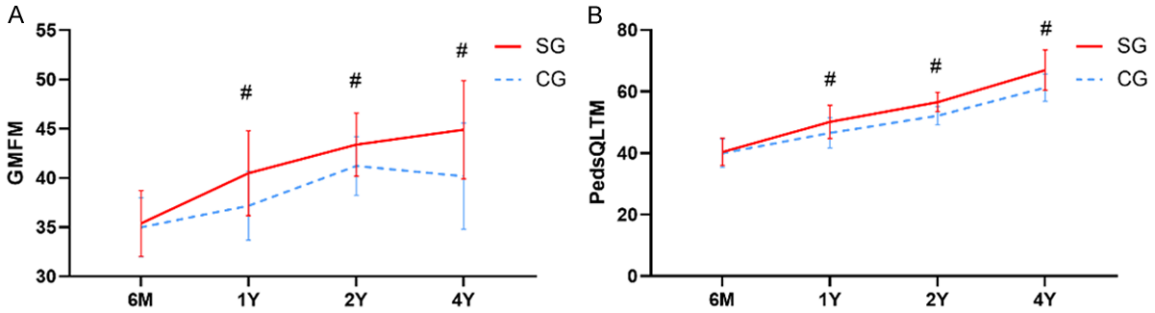


**Figure 4.** Changes in gross motor function and quality of life. A: Gross motor function. B: Quality of life. Compared to the control group, $^{\#}P < 0.05$.

**Table 7.** Univariate analysis of risk factors affecting surgical outcome

| General data | | Valid (n=76) | Invalid (n=9) | $t/\chi^2$ | *P* |
|---|---|---|---|---|---|
| Gender | Male | 49 | 4 | 1.375 | 0.241 |
| | Female | 27 | 5 | | |
| Age | > 1 month | 20 | 8 | 14.263 | < 0.001 |
| | < 1 month | 56 | 1 | | |
| Mean weight (kg) | | 2.99±0.11 | 3.03±0.18 | 0.957 | 0.341 |
| Urination and defecation dysfunction | Yes | 70 | 7 | 1.937 | 0.164 |
| | No | 6 | 2 | | |
| Nerve damage | Yes | 35 | 4 | 0.008 | 0.927 |
| | No | 41 | 5 | | |

**Table 8.** Logistic regression analysis of risk factors affecting surgical outcome

| Variable | β | SE | Wald | 95% CI | *P* |
|---|---|---|---|---|---|
| Gender | 0.034 | 0.114 | 0.105 | 0.891-1.219 | 0.781 |
| Age | 0.871 | 0.371 | 2.817 | 0.819-4.381 | 0.012 |
| Urination and defecation dysfunction | 0.293 | 0.145 | 2.111 | 0.617-1.092 | 0.172 |
| Nerve damage | 0.435 | 0.281 | 1.289 | 0.819-1.112 | 0.213 |

tries in the same period of time. The incidence of CNTD was reduced to 11.95 per 10,000 in 2000 by means of folic acid intake during pregnancy, with remarkable results [19]. Although the incidence of CNTD has decreased, the treatment is still the focus of current medical research. The traditional treatments for neural tube defects include ligation of the protruding meningeal sac, cerebrospinal fluid shunt, and myelomeningocele repair. Although the survival rate of children has been improved to a certain extent, the neurological dysfunction is not completely improved [20].

In recent years, with the continuous progress in microscopic technology, the application of microscopic instruments for spinal cord embolization has gradually emerged in clinical practice. In this study, 42 newborns with CNTD who underwent early spinal cord embolization were included as a study group (SG), and 43 children who received spinal cord embolization later were included as a control group (CG). The differences in clinical efficacy between the two groups were compared with regard to the short-term efficacy. The results showed that the total effective rate was 93.02% in SG and 85.71% in CG, and the difference between the two groups was not statistically significant, while in the long-term efficacy, the total effective rate was 88.37% in SG and 69.05% in CG, with SG showing significantly better efficacy than CG. A clinical study of 45 children with CNTD found that 89% of children had progressive neurological impairment after meningocele repair alone [21]. In a study of 12 cases of myelomeningocele, all patients had symptoms of tethered cord after simple resection of superficial lipoma [22]. It was concluded that although the survival rate of children with CNTD improved significantly after meningocele repair, spinal cord injury due to neural tube injury did not improve, and the spinal cord gradually progressed to spinal cord insufficiency under the mechanical strain of the end filaments, resulting in lower limb paralysis, incontinence, and clubfoot [23]. If a child has a late release of tethered spinal cord, the clinical symptoms may continue to aggravate due to the compression of the cyst during the growth process. The authors of the present study also found that the treatment of CNTD should not be limited to morphological features. The repair of the patient's neurological function is an important factor in improving the prognosis of patients.

In this study, the release grading of the two group was analyzed, and the results found that 93.02% of the newborns in SG had grade 1 release after meningocele repair and only 6.98% had grade 2 release, while CG had much worse release than SG, which is similar to the findings of other scholars. A clinical study of 56 children with CNTD showed that there were 94.60% of children with grade 1, 3.50% with grade 2, and 1.8% with grade 3 after meningocele repair [24]. To further demonstrate the long-term results of meningocele repair, the motor function and quality of life were also compared, and the results showed that the differences in these indicators between the two groups were not significant in the short term, but the motor function and quality of life of newborns in the SG were significantly better than those in the CG from 1 to 4 years after surgery. We believe that the purpose of meningocele repair was to remove the lesion and release the embolus, and that the removal of the lesion improved the secondary damage caused by nerve compression and bulge, while the release of the embolus allowed the removal and stripping of the adherent tissue and the complete release of the spinal cord, which laid a solid foundation for the preservation and even the recovery of neurological function [25].

In fact, although a number of studies have proven that meningocele repair can effectively prevent further aggravation of nerve damage, it is not effective for established nerve damage, and in recent years, nerve repair modalities such as stem cell therapy and molecular therapy have been gradually emphasized. It has been reported that chicken embryo models of NTD can be obtained by surgical disruption of neural tube closure, and human embryonic stem cells can be injected into them to produce neural tube reclosure, which confirms that stem cell therapy is more feasible in animal models [26]. It was also found that in sheep models, neurohepatocytes would localize to the site of spinal cord injury by migration and exert a repair effect [27], which provides new ideas for the treatment of neural tube defects. Finally, univariate and multivariate logistic regression analysis was conducted on the risk factors affecting the surgical outcome of children, and the results showed that age > 1 month was an independent risk factor for poorer surgical outcome. This may be due to the fact that children with older age usually have

complications such as urinary tract infection and urinary retention caused by the illness. Prolonged nerve stretch may cause significant neurological ischemia and hypoxia symptoms in children, and their preoperative neurological function is prone to obvious damage. Even if surgery is performed, it is often difficult to achieve the desired results. Therefore, early surgery is recommended for such children.

In conclusion, microsurgery had a good short-term and long-term intervention effect on children with CNTD, and the newborns had an improvement in postoperative long-term motor function and quality of life. It is recommended that meningocele repair combined with spinal cord release should be performed within 30 d after birth, and early intervention can effectively improve the effectiveness of treatment. The novelty of this study is the inclusion of newborns with CNTD of different ages to demonstrate the optimal timing of meningocele repair to improve the prognosis of newborns with CNTD. The shortcomings of this study include, first, the small sample size, which may be related to the rarity of newborns with CNTD, and second, the limited data studied and the lack of analysis of the mechanisms associated with interventions for children with CNTD, which will be improved at a later stage.

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## Disclosure of conflict of interest

None.

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