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Clinical evaluation of enhanced recovery after surgery protocol for anterior cervical decompression and fusion (ACDF): study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction To improve the efficacy of anterior cervical decompression and fusion (ACDF) and reduce postoperative complications in degenerative cervical myelopathy, our team established a set of perioperative care of enhanced recovery guidelines of ACDF based on the concept of enhanced recovery after surgery. In addition, a prospective, multicentre, randomised clinical trial was designed.

Methods and analysis A total of 260 patients aged 18–65 years will be included. Preoperative MRI and CT will be used to confirm the typical manifestations of cervical spondylosis, such as cervical disc herniation and spinal cord compression. The patient presents with neck and shoulder pain, numbness of upper limbs, weakened grip strength and cotton sense of foot tread. Patients received normal conservative treatment for 3 months with no obvious relief or even aggravation of symptoms. Patients will be assigned to the group in strict accordance with the random allocation table. Patients in groups A and B will receive conventional perioperative care and perioperative care for enhanced recovery, respectively. The main outcome indicators are the Karnofsky Performance Scale score and the Japanese Orthopaedic Association scale. Secondary outcome indicators are pain assessment by Numeric Rating Scale, Neck Disability Index, quality of life index (QL-Index) and postoperative complications. Follow-up will be conducted at 3, 6 and 12 months postoperatively.

Ethics and dissemination Ethical approval has been granted by the Ethics Committee of Fujian Medical University Union Hospital, Fuzhou, China (2020YF034-01). Results of the research will be published in an international peer-reviewed scientific journal and disseminated through presentation at scientific conferences.

Trial registration number ChiCTR2000040508.

Strengths and limitations of this study

- Large, multicentre, pragmatic, randomised controlled trial designed to evaluate the efficacy of conventional perioperative care and perioperative care of enhanced recovery in the patients of anterior cervical decompression and fusion.
- Use of standardised and validated outcome instruments.
- In different stages of this study, special personnel will be assigned to take charge of related work.
- Due to time constraints, the follow-up time of this study will be only 1 year.

INTRODUCTION

Degenerative cervical myelopathy (DCM) is caused by direct compression of the spinal cord or inadequate local blood supply to the spinal cord. A significant aetiology is cervical stenosis as it can be congenital or mostly secondary stenoses. Disc herniation, ligamentum flavum folding and osteophytes can all result in reduced cervical canal space.[1] DCM is causing progressive disability and affecting the quality of life.[2 3] The characteristic symptoms and signs of DCM include loss of flexibility of the hand, decreased muscle strength, stiffness of the limbs, urination urgency, frequency or hesitation of urination, limb spasm and gait disorder (including stiff or spastic gait).[4 5] The conservative treatment of DCM usually includes neck support braking, analgesic drugs, epidural hormone injection, nerve root block, facet joint closure, facet joint drenching.[5–7] Traction and massage may cause further compression of the spinal cord, so it should be prohibited.[8] Progression of neurological dysfunction and changes in spinal cord signals on T2-weighted MRI are clear indications for surgery. The purpose of the procedure is to relieve the compression of the spinal cord and restore the normal curvature of the cervical spine.

Smith and Robinson described anterior cervical decompression and fusion (ACDF)

in 1958. This surgical approach is still the standard surgical approach for the treatment of cervical disc herniation.[9] Anterior cervical surgery, through extensive removal of the disc, can directly decompress the spinal cord and bilateral nerve roots, as well as facilitate the implantation of artificial discs or other artificial fusion materials. First proposed by Henrik Kehlet in 1997, the enhanced recovery after surgery (ERAS) is a series of perioperative optimisation measures based on evidence-based medicine to reduce the physiological and psychological traumatic stress during perioperative period, reduce complications and accelerate recovery.[10] This is a multidisciplinary, multimodal approach.[11] ERAS has been successfully applied in general surgery, cardiothoracic surgery, obstetrics and gynaecology, orthopaedic joint replacement surgery and other fields.[12] In recent years, it has been gradually developed in the field of spinal surgery and accepted by more spinal surgeons.[13] Although the treatment of DCM with ACDF has the advantages of small incision and surgical trauma, the incision is adjacent to important nerve vessels, and the tissue structure is complex, thus posing certain surgical risks and surgical complications. In addition, postoperative complications such as hoarseness and swallowing discomfort are often caused by intraoperative tractive trachea and implantation of plate internal fixation materials.[14] To improve the efficacy of ACDF and reduce postoperative complications, the team established a set of perioperative care of enhanced recovery (PCER) guidelines of ACDF based on the concept of ERAS. PCER is designed to increase the perioperative nutrition intervention, preoperative intervention of early rehabilitation training, intraoperative strengthening of heat preservation, postoperative change of routine rehabilitation training mode, such as increasing the use of rehabilitation training equipment, self-made training exercises, etc., in order to promote the rapid recovery of patients after surgery, to achieve satisfactory nursing efficacy. The arising amount of data showing that the use of ERAS programmes could be helpful in reducing the days of hospitalisations and the number of complications for cervical spine surgery in a highly selected group of patients also highlight the current lack of high level of scientific evidence.[15] Therefore, a prospective, multicentre, randomised clinical trial has been designed, in which patients receiving ACDF will be randomly divided into two groups and PCER and conventional perioperative care (CPC) will be applied to explore the nursing effect of PCER in patients receiving ACDF treatment.

METHODS AND ANALYSIS

Study description

This study is a prospective, multicentre, non-inferiority randomised controlled trial (RCT) to compare the nursing effect difference between CPC and PCER for patients treated with ACDF. The follow-up period will continue for 1 year. The actual intervention will be concealed from the subjects and follow-up researchers until the end of the follow-up period. The main assessment indicators are Karnofsky Performance Scale (KPS) score and Japanese Orthopaedic Association (JOA) score. Table 1 shows the time points of screening, randomisation and evaluation in detail.

Participant recruitment and eligibility

The participant will be conducted on a voluntary basis, so only after each appropriate patient agrees to participate and

Table 1 Flow chart visits and case report forms

Time for evaluation	Screening period	Intervention period	Evaluation period 1	Evaluation period 2	Evaluation period 3	Evaluation period 4
Assessment	Screen	Randomisation	Hospital discharge	3 months following treatment	6 months following treatment	12 months following treatment
Eligibility screen	√					
Informed consent	√					
Demographic information	√					
Admission health education	√					
Auxiliary inspection guide	√	√	√	√	√	√
Preoperative guidance		√				
Intraoperative care		√				
Postoperative nursing		√	√			
Nursing document writing	√	√	√			
Occurrence of complications		√	√	√	√	√
Discharge guidance			√			
Nursing adverse events	√	√	√			
Cervical functional assessment	√		√	√	√	√

signs the informed consent, they will be placed on the waiting list. Detailed inclusion and exclusion criteria are as follows.

Inclusion criteria

1. Aged 18–65 years.
2. Preoperative MRI and CT confirmed signs of cervical disc herniation and compression of spinal cord.
3. Typical manifestations of cervical spondylosis, such as neck and shoulder pain, numbness of both upper limbs, weakened grip strength and cotton feeling on the feet.
4. Normal conservative treatment for 3 months, no obvious relief or even worse symptoms.
5. No absolute surgical contraindication.
6. Informed and consented.

Exclusion criteria

1. With a history of cervical spine surgery.
2. Congenital spinal stenosis or cervical deformity.
3. With dysphagia before surgery.
4. With infection and tumour.
5. Expected survival time is less than 1 year.
6. With language communication disorder.
7. Participating in other clinical trials.
8. With rheumatic immune diseases that may cause similar symptoms.
9. Not suitable for MRI, CT and other special examinations.

Patient and public involvement statement

The patients and the public were not (or will not) be involved in the design, or conduct, or reporting or dissemination of the research.

Randomisation and blinding

A completely randomised scheme will be used in this study. After signing the written consent, the randomisation specialist will import the patient information into the EDC system after the patient's enrolment is confirmed by the enrolment specialist. The EDC system will randomly assign the patients to PCER or CPC, and the random results will be sent to the designated mailbox. The responsible nurses will provide perioperative nursing according to the assigned results. A double-blinded design will be used in this study, for follow-up specialists and statistical specialists as well as for patients and research assistants. However, the responsible nurse has the right to know about the grouping of patients.

Interventions

Patients will be randomly assigned to the CPC and PCER groups. The common treatment measures for the two groups from admission to follow-up are as follows.

1. Health education on admission: the introduction of the chief physician and the responsible nurse; guidance on the environment, facilities and safety management of wards and advice on quitting smoking and drinking.
2. Guidance on matters requiring attention during the preoperative examination.
3. Perioperative assessment: routine nursing risk assessment, including assessment of nutritional status (NRS2002 table), inpatient fall bed/fall risk assessment, pressure ulcer risk assessment (Braden scale), thrombosis risk assessment (Caprini scale), the function of daily life activities condition assessment (Barthel table), sleep assessment (PSQI scale) and pain assessment (Numeric Rating Scale, NRS), Quality of Life Index (QL-Index). Specialist spine assessment: cervical spine dysfunction assessment (Neck Disability Index, NDI scale); neck muscle strength assessment: freehand muscle strength test (MMT), neck range of motion measurement, JOA score, KPS score, etc.
4. Preoperative preparation: cervical overextension training and guidance for the wearing of a neck brace, the handling of personal hygiene, the preparation of effective cough and sputum, and the preparation of necessary surgical items.
5. All patients will undergo ACDF under general anaesthesia.
6. Intraoperative nursing: the temperature between operations should be kept at 25°C; the patient's body temperature will be monitored at the beginning and after the operation and catheterisation will be performed after general anaesthesia.
7. Postoperative care: the patients will be given grade I care, ECG monitoring and low-flow oxygen inhalation when they return to the ward on the day of operation. The respiratory tract will be kept unblocked and we will closely observe the changes in the patient's respiratory frequency and rhythm. Oozing fluid at the incision sight will be monitored; medical treatment will be given as advised.
8. Discharge: the patients will be given diet guidance, rest and activity guidance, discharge medication guidance, return visit guidance and rehabilitation exercise guidance.
9. Follow-up: follow-up will be conducted at 3, 6 and 12 months after surgery, including cervical spine dysfunction assessment (NDI scale), cervical mobility measurement, JOA cervical spine score, KPS functional status assessment and life quality score (QL-Index) to understand the incidence of complications.

Patients in CPC group and PCER group received different nursing programmes, as shown in the table 2.

Baseline assessment

Baseline records will include demographic, admission diagnosis, admission time, operation time, discharge time, postoperative length of stay, cost, etc.

Outcomes assessment

The following validated outcome measures will be used in the form of a questionnaire to evaluate the efficacy of nursing care.

Table 2 Difference in intervention between CPC group and PCER group

Time	CPC group	PCER group
On admission	**Admission health education**	**Admission health education**
	/	□Pelvic floor muscle training (levator anal training)
	Diet	**Diet**
	□Regular diet	□Healthy diet: high in protein and coarse fibre; low in fat; avoid spicy irritation
	Psychological assessment	**Psychological assessment**
	/	□Assessed by SAS scale
Preoperative day	**Oral care**	**Oral care**
	□Brush teeth (using a toothbrush)	□Brush teeth (using a toothbrush)+gargle (cipiromonium chloride gargle)
	Protect lung intervention	**Protect lung intervention**
	□Guidance on deep breathing and cough effectively	□Breath trainer machine
	/	□Atomisation two times per day or three times a day
	Preoperative rehabilitation training guidance	**Preoperative rehabilitation training guidance**
	□Position training: neck overextension	□Position training: neck overextension +axis turn
	/	□Trachea push–pull training
	Diet	**Diet**
	□Regular diet	□One day before surgery, choose the diet according to the diet provided
	□No food or drink after 22 o'clock	□800 mL of 12.5% carbohydrate was taken oral administration 12–13 hours before surgery
	/	□400 mL of 12.5% carbohydrate was taken oral administration 2–3 hours before surgery
In the operation	**Intraoperative insulation**	**Intraoperative insulation**
	□Room temperature 25°C	□Room temperature 25°C+insulation blanket
On the day of surgery	**Diet**	**Diet**
	□Fasting	□400 mL of 12.5% carbohydrate was taken oral administration 6 hours after surgery
	Position guidance	**Position guidance**
	□Fix both sides of neck with sandbags	□Neck limiter
	Pain management	**Pain management**
	□Use painkillers when the patient is in pain	□Use of non-steroidal analgesics (carmine)
	Oral care	**Oral care**
	□Gargle with warm water	□Gargle with cipiromonium chloride gargle

Continued

Table 2 Continued

Time	CPC group	PCER group
The first day after surgery—the day before discharge	**Diet**	**Diet**
	□Transition from liquid to normal diet.	□Nutritional powder was taken on the first day after surgery, and then a normal diet was transitioned
	Position guidance	**Position guidance**
	□Fix both sides of neck with sandbags	□Neck limiter
	Oral care	**Oral care**
	□Brush teeth (using a toothbrush)	□Brush teeth (using a toothbrush)+gargle (cipiromonium chloride gargle)
	Breathing training	**Breathing training**
	□Guidance on deep breathing and cough effectively	□Breath trainer machine
	Time to get out of bed	**Time to get out of bed**
	□Proceed according to actual situation	□48 hours later (the second day after surgery)
	/	□Psychological support and encouragement for getting out of bed
	Catheter removal time	**Catheter removal time**
	□Proceed according to actual situation	□24 hours after surgery
	Rehabilitation exercise	**Rehabilitation exercise**
	□Prevention of VTE:[22] families assist in active +passive sports	□Prevention of VTE: use mini lower extremity trainer
	□Active activities of upper limbs	□Neck muscle relaxation
	□Bedside activities	□Thermal application of trapezius (infrared radiation) and massage
	The wound	**The wound**
	□Use infrared irradiation when poor healing occurs	□Infrared radiation (from the first day after surgery)

CPC, conventional perioperative care; PCER, perioperative care of enhanced recovery; SAS, Social Anxiety Scale; VTE, Venous Thrombus Embolism.

Primary outcome measures

1. Karnofsky score (KPS)[16]

The higher the KPS score, the better the health, the more tolerable the side effects of the treatment, and therefore, the more likely the patient is to undergo thorough treatment. It is generally believed that a KPS score above 80 is independent, that is, independent in daily living. A score of 50–70 is classified as semi-independent, that is, semi-independent living. A score below 50 is dependent.

2. Japanese Orthopaedic Association (JOA)[17 18]

The JOA scale will be used to assess neurological function. JOA scores at admission, after surgery, before discharge and during follow-up will be recorded. The full score is 17, and the postoperative improvement rate will be calculated as follows: ((postoperative total score−preoperative total score)/(17−preoperative total score))×100%; improvement rate:≥75%, excellent; 50%–74%, good; 25%–49%, medium; 0%–24%, poor.

Secondary outcome measures

1. Numeric Rating Scale (NRS)[19]

Pain assessment with the NRS: 0–10 is used to represent different degrees of pain in the numeric rating method. The pain rating standard is 0, painless; 1–3, mild pain; 4–6, moderate pain 7–10, severe pain.

2. Neck Disability Index (NDI)[20]

NDI is commonly used clinically to assess the cervical spine functional status. The scale includes 10 aspects: pain, personal care, lifting, reading, headache, attention, work, driving, sleep and recreation. Each item is five points and the score ranges from 0 (barrier-free) to 50 (complete paralysis); the higher the score, the worse the dysfunction. Cervical spine functional impairment index (%) = (total score per project/number of completed projects×5)×100%. The results were 0%–20%, indicating mild dysfunction; 20%–40%, indicating moderate dysfunction; 40%–60%, severe dysfunction; 60%–80%, very severe dysfunction and 80%–100%, complete dysfunction or should be carefully checked for exaggerated symptoms.

3. Quality of Life Index (QL-Index)[21]

QL-Index, is designed by Spitzer in 1981, is a simple scale that can quickly evaluate patients' quality of life and help estimate the treatment effect of severe diseases and the degree of disease alleviation. The scale consists of five aspects: activity, daily life, health, support and general situation, with three levels of 0.1.2 for each item. Choose the most appropriate column item by item according to the patient's current situation, and record the corresponding score. QL-Index=Activity Score +Daily Life Score +Health Score +Support Score +General Situation Score. The total score ranged from 0 to 10, with a high score of 10 and a low score of 0. Those with high scores had a better quality of life than those with low scores: 0–3 was a very low score. The best was a trend analysis: an increase in scores suggested improvements in quality of life. Decreased scores indicate a deterioration in quality of life.

4. Postoperative complications

There are two main types of postoperative complications. Early surgical postoperative complications including postoperative haematoma; tissue swelling; dural tear/CSF leakage; voice hoarseness/difficulty swallowing; nerve root palsy (transient/permanent); injury to vascular structures, trachea, oesophagus and spinal cord; surgical site infection (superficial or deep). Late surgical complications including adjacent disc disease; progressive cervical kyphosis; implant pullout/subsidence; aseptic discitis and medical complications including urinary tract infection; upper respiratory tract infection; deep vein thrombosis/pulmunary embolism; myocardial infarct; stroke; death.

Sample size

In this study, the sample size was calculated according to α=0.05, β=0.2, sample ratio 1:1, and the JOA score of 150 patients with DCM from 2017 to 2019 in our hospital at 1 year after surgery was taken into account, μA=15.5, μB=15.1, σ=1.1. A total of 95 samples were calculated for each group. When the shedding rate was set at 20%, the final sample size was 238 cases. According to the actual situation of each centre, 260 subjects will be included in this study. We expect to complete subject recruitment within 2 years. Subjects will be recruited on 1 January 2021.

Statistical analysis

Both sets of baseline data will include demographic information, general conditions prior to intervention and baseline indicators that may influence prognosis. The mean, SD and CI of the measurement data will be given, and the minimum, maximum, P25, median and P75 will be provided when necessary. Measurement data shall be tested by t-test or a non-parametric t-test (when variance is uneven); the Pearson2 test will be used for counting data; Wilcoxon two-sample rank sum test will be used for grade data. The Pearson2 test will be used to compare the incidence of adverse events between the two groups. A p value less than 0.05 will be considered statistically significant. The analysis will be performed using appropriate statistical software, such as SPSS.

ETHICS AND DISSEMINATION

This article describes a protocol for a prospective, non-inferiority RCT to examine the efficacy of CPC and PCER in the patients of ACDF. Informed consent will be obtained prior to randomisation from all eligible participants (online supplemental appendix 1). Results of the research will be published in an international peer-reviewed scientific journal and disseminated through presentation at scientific conferences.

Contributors All authors are the principal investigators and have coordinated all the phases of trial design, statistical analysis plan and drafting of the protocol. G-QZ, Y-JL and CC completed the conception and design of the project. BL and ZL carried out the acquisition of data or analysis and interpretation of data. BL, RQL

and ZL wrote the manuscript. All authors contributed to refinement of the study protocol and approval of the final manuscript.

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REFERENCES

1 Parke WW. Correlative anatomy of cervical spondylotic myelopathy. *Spine* 1988;13:831–7.
2 Theodore N. Degenerative cervical spondylosis. *N Engl J Med* 2020;383:159–68.
3 King JT, McGinnis KA, Roberts MS. Quality of life assessment with the medical outcomes study short form-36 among patients with cervical spondylotic myelopathy. *Neurosurgery* 2003;52:113–20.
4 Denno JJ, Meadows GR. Early diagnosis of cervical spondylotic myelopathy. A useful clinical sign. *Spine* 1991;16:1353–5.
5 Bakhsheshian J, Mehta VA, Liu JC. Current diagnosis and management of cervical spondylotic myelopathy. *Global Spine J* 2017;7:572–86.
6 Fehlings MG. Current knowledge in degenerative cervical myelopathy. *Neurosurg Clin N Am* 2018;29:xiii–xiv.
7 Ganau M, Holly LT, Mizuno J, *et al*. Future directions and new technologies for the management of degenerative cervical myelopathy. *Neurosurg Clin N Am* 2018;29:185–93.
8 Yoo JU, Zou D, Edwards WT, *et al*. Effect of cervical spine motion on the neuroforaminal dimensions of human cervical spine. *Spine* 1992;17:1131–6.
9 Smith GW, Robinson RA. The treatment of certain cervical-spine disorders by anterior removal of the intervertebral disc and interbody fusion. *J Bone Joint Surg Am* 1958;40-A:607–24.
10 Joliat G-R, Labgaa I, Petermann D, *et al*. Cost-Benefit analysis of an enhanced recovery protocol for pancreaticoduodenectomy. *Br J Surg* 2015;102:1676–83.
11 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997;78:606–17.
12 Nygren J, Thacker J, Carli F, *et al*. Guidelines for perioperative care in elective rectal/pelvic surgery: enhanced recovery after surgery (ERAS®) Society recommendations. *Clin Nutr* 2012;31:801–16.
13 Tiansheng S, Jianxiong S, Zhongjun L. Expert consensus in enhanced recovery after spinal surgery in China：perioperative management. *Chinese Journal of Bone and Joint Surgery* 2017;10:271–9.
14 Fountas KN, Kapsalaki EZ, Nikolakakos LG, *et al*. Anterior cervical discectomy and fusion associated complications. *Spine* 2007;32:2310–7.
15 Zaed I, Bossi B, Ganau M, *et al*. Current state of benefits of enhanced recovery after surgery (ERAS) in spinal surgeries: a systematic review of the literature. *Neurochirurgie* 2021;S0028-3770(21)00107-7. doi:10.1016/j.neuchi.2021.04.007. [Epub ahead of print: 23 Apr 2021].
16 Terret C, Albrand G, Moncenix G, *et al*. Karnofsky performance scale (KPS) or physical performance test (PPT)? that is the question. *Crit Rev Oncol Hematol* 2011;77:142–7.
17 Kato S, Oshima Y, Oka H, *et al*. Comparison of the Japanese orthopaedic association (JOA) score and modified JOA (mJOA) score for the assessment of cervical myelopathy: a multicenter observational study. *PLoS One* 2015;10:e0123022.
18 Martin AR, Jentzsch T, Wilson JRF, *et al*. Inter-Rater reliability of the modified Japanese orthopaedic association score in degenerative cervical myelopathy. *Spine* 2021;Publish Ahead of Print. doi:10.1097/BRS.0000000000003956. [Epub ahead of print: 22 Jan 2021].
19 Hawker GA, Mian S, Kendzerska T, *et al*. Measures of adult pain: visual analog scale for pain (vas pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CpGs), short Form-36 bodily pain scale (SF. *Arthritis Care Res* 2011;63:S240–52.
20 Vernon H, Mior S. The neck disability index: a study of reliability and validity. *J Manipulative Physiol Ther* 1991;14:409–15.
21 Spitzer WO, Dobson AJ, Hall J, *et al*. Measuring the quality of life of cancer patients. *J Chronic Dis* 1981;34:585–97.
22 Chibbaro S, Cebula H, Todeschi J, *et al*. Evolution of prophylaxis protocols for venous thromboembolism in neurosurgery: results from a prospective comparative study on low-molecular-weight heparin, elastic stockings, and intermittent pneumatic compression devices. *World Neurosurg* 2018;109:e510–6.