Clinical Neurology and Neurosurgery 182 (2019) 5–10

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

The use of $CaSO_4$ drug delivery system in transforaminal lumbar interbody fusion for spinal brucellosis

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ARTICLE INFO

Keywords:
Spinal brucellosis
TLIF
Drug delivery system

ABSTRACT

Objectives: The incidence of human brucellosis has risen dramatically in China with few reports regarding the operation on spinal brucellosis. In this retrospective study we introduced $CaSO_4$drug delivery system into the TLIF surgical procedure and evaluated its clinical effectiveness and feasibility.

Patients and Methods: 36 patients with lumbar brucellosis were enrolled and treated by posterior transforaminal decompression, instrumentation and fusion. Prepared $CaSO_4$ beads carrying doxycycline were placed into the disc space and around pedicle screws. The activity of infection and pain-related function scales were recorded. Neurologic and functional recovery was evaluated using ASIA and Kirkaldy-Willis scale. Segmental and overall lordotic angles were measured and fusion status was assessed at final follow up.

Results: The average follow-up period was 15.6 ± 3.73 months. The level of ESR and CRP returned to normal at 3 months post-op. 14 patients with ASIA grade D pre-op returned ASIA grade E with 3 months. The improvement of VAS and ODI was 82% and 85.8% at 3 months post-op. The corrections of segmental and overall lordotic angle were 5.98 ± 3.54° and 6.24 ± 7.93°. 69% of patients reached definitive union at 12 months after surgery. The satisfactory rate on Kirkaldy-Willis functional outcome criteria was 88.9%.

Conclusion: The use of $CaSO_4$ drug delivery system during single-stage TLIF for spinal brucellosis was safe and showed no negative impacts on fusion status and neurological function recovery. Our results are promising and the drug delivery system may be considered as a choice for future treatment in spinal brucellosis or other spondylodiscitis.

1. Introduction

Brucellosisis a systemic zoonotic infection mainly reported in the Mediterranean region in literature. In China the incidence of human brucellosis has risen dramatically since 21st century. The disease is endemic in 25 of 32 provinces and most cases were reported in peasants and herdsmen with direct contact with infected animals, predominantly sheep and goat [1]. Spinal brucellosis is defined as the involvement of spinal column, interspinal spaces, and/or paraspinal areas, which is observed in 6–12% of cases in brucellosis [2]. It is the prevalent clinical form in adults and elderly patients and the foremost cause of debilitating and disabling complications. Despite many features obtained from MRI, it remains quite difficult to distinguish spinal brucellosis from tuberculosis and other pyogenic spondylodiscitis cases through regular radiology tests [3]. Serology test is the golden diagnostic method with serum agglutinin titers of ≥ 1:160 as a positive result.

Conservative therapy based on antibiotics is the mainstay of spinal brucellosis. The World Health Organization (WHO) released treatment recommendations for human brucellosis in 1986 and the regimen was re-discussed in 2007 in Ioannina, Greece [4]. The optimal treatment of uncomplicated brucellosis should be based on a six-week regimen of doxycycline combined with either streptomycin or rifampicin. Surgery is considered in patients with epidural abscess and neurologic deficits. However, some patients responded only partially to antibiotics or required several courses of treatment [5]. In patients with spinal involvement of brucellosis, the long duration of antibiotic treatment was usually accompanied with long time of immobilization, which resulted in poor quality of life. Thus the role of surgery in spinal brucellosis remains controversial in patients with no or minor neurologic symptoms.

The surgical procedures for spinal brucellosis reported in literature include percutaneous or open abscess drainage, laminectomy, transpedicle discectomy and fusion with anterior or posterior approach. Most of them could relieve the spinal cord from compression of abscess and obtain samples helpful for final diagnosis. The use of instruments in spinal infection has been a matter of debate for decades, while its use of

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https://doi.org/10.1016/j.clineuro.2019.04.022
Received 5 November 2018; Received in revised form 22 April 2019; Accepted 24 April 2019
Available online 26 April 2019
0303-8467/

in spinal brucellosis has rarely been reported in literature. However, if the stability of spine was endangered from either the infective process or debridement procedure, stabilizing the spine with instrumentation and fusion may serve as a last resort [6]. It was also interesting to find that surgery with instrumentation may be more beneficial in terms of improving the quality of life in some patients with spinal infection [7].

In the treatment of osteomyelitis after infection, the efficacy of systemic antibiotics may be limited by impaired blood flow of infected bone, or interspinal spaces, especially in spondylitis. As a result of this, local administration of antibiotics has been proposed to serve as an adjunctive therapy to parenteral and oral antibiotics. Different drug delivery systems have been developed to serve producing prolonged high antibiotic concentrations at the site of infection and filling dead space of bone. Of all these systems, the delivery systems based on calcium sulphate ($CaSO_4$) have been reported to serve in treatment of different chronic bone infections [8,9]. However, there has been no research reporting the use of such systems in treatment of brucellosis. Considering that there are definitive recommendations antibiotics regimen for brucellosis, we believe that it is promising to explore the application of these drug delivery systems in the surgical procedures for spinal brucellosis.

In the present study, we retrospectively reviewed 36 patients who had been treated with single-stage posterior-lateral transforaminal decompression, debridement and fusion with instrumentation for spinal brucellosis. During the surgery procedure, doxycycline was delivered into interspinal space by $CaSO_4$drug delivery system. The results in terms of cure of disease pathology, pain relief, improvement of neurologic function and correction of sagittal alignment were analyzed to determine the clinical effectiveness and feasibility of this surgical procedure.

2. Patients and methods

2.1. General information

Between January 2014 and December 2016, 84 patients with lumbar spinal brucellosis were treated by our group in Qilu hospital. Initial diagnosis was based on the clinical presentation as persistent low-back pain and fever, history of direct contact with livestock, as well as signs consistent with infection on digital radiography, computed tomography (CT) and magnetic resonance imaging (MRI). Confirmed diagnosis was made by the standard tube agglutination test for Brucella antibodies $\geq$1/160 and/or isolation of Brucella species from blood samples. Sixty-four patients were recommended for conservative therapy as oral antibiotics, bed rest and bracing alone, among whom forty-eight of these patients responded properly while the symptom of the other sixteen patients persisted or worsened and required surgery (indirect recruited group). Twenty patients were recommended surgery at first confirmed diagnosis (direct recruited group). In this way, this retrospective study included 36 patients for surgery all together (Table 1). There were 26 males and 10 females respectively, aged from 34 to 73 (mean 50.72 ± 10.39). All patients had lumbar spine spondylodiscitis involvement with 5 patients at L1-2, 11 at L2–3, 6 at L3-4, 9 at L4-5 and 5 at L5/S1 (Fig. 1). None of the cases in this study had involvement of multilevel interspaces.

The indications for surgery included the presence of obvious neurologic deficit attributed to nerve root compression by epidural abscess or inflammatory granuloma at diagnosis or during conservative therapy, definite evidence of spinal instability caused by vertebral or disc destruction, persisted severe back pain despite adequate antibiotic therapy ($\geq$6 weeks).

2.2. Operative procedure

All the surgeries were performed on a four-poster spinal frame in prone position under general anesthesia. A middle line incision was made to expose posterior spinal elements. The preparation of the $CaSO_4$ drug delivery system involved mixing doxycycline 200 mg in powder form, 5 ccs $CaSO_4$hemyhydrate and 10 ml deionized water in the product set (Stimulan®). The mixedpaste was then poured into a mold to produce spherical beads of different sizes after dessication. The setting time taken for conversion from hemihydrate to dihydrate varied from 10 to 15 minutes, depending on the volume of $CaSO_4$. The pedicle screws were inserted into both sides of the involved vertebra level with the prepared $CaSO_4$beads placed around screws. A temporary rod was placed on screws on the less involved side to stabilize the surgery region and facetectomy was then performed on the other side. The epidural abscess was drained, the involved disc, end plates and soft granulation tissues were debrided. The abscess fluid and removed tissues were sent for bacteria culture, antibiotic sensitivity test, as well as histopathologic examination. If the radiologic or neurologic manifestation involved both sides, the same debridement was also performed on the opposite side. The debrided disc space was rinsed sufficiently with hydrogen peroxide and normal saline. After final preparation of the upper and lower bony recipient site, the prepared $CaSO_4$beads (Fig. 2) were placed into the anterior half of the disc space and autologous iliac bone graft was implanted into the posterior half for interbody fusion. Pre-contoured rods were placed on the screws of both sides under proper compression. Drainage was performed for two days postoperatively.

Table 1
Demographic information of all patients.

	Number	Percentage of patients
Sex		
male	26	72.2
female	10	27.8
Age		
31-40	8	22.2
41-60	24	66.7
61-80	4	11.1
Segment		
L1/2	5	13.9
L2/3	11	30.6
L3/4	6	16.7
L4/5	9	25
L5/S1	5	13.9
Fever	26	72.3
Positive on Culture	10	27.8
ASIA scale		
D	14	38.9
E	22	61.1
Follow-upperiod	average 15.6 months	

2.3. Postoperative management

Intravenous antibiotic (a second-generation cephalosporin) was given for the first 24–48 h after surgery until the drainage was removed. Then all patients were administered an oral antibiotic treatment according to the Ioannina recommendations, which consisted of doxycycline 100 mg twice daily and rifampicin 900 mg daily, for a minimum 8 weeks after surgery. All patients remained bed rest for 5–7 days and then were mobilized wearing a frametype lumbosacral brace for 2–3 months after surgery.

2.4. In-hospital and follow-up evaluation

Patients' data were recorded before 2 days before surgery (this time point was same for the 16 patients in indirect recruited group) and 7 days after surgery in hospital. Then they were followed-up at 1, 3, 6 months and then annually. Laboratory data, radiographic studies, neurologic and functional scales were recorded and analyzed. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values of direct and indirect recruited group before surgery to rule out

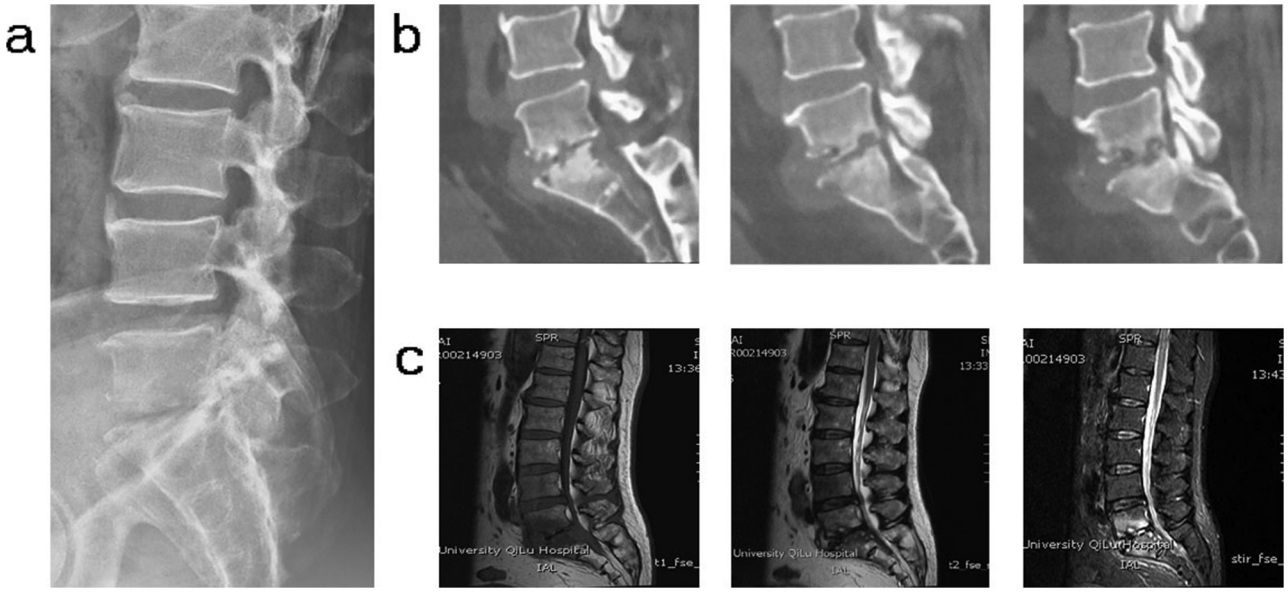

Fig. 1. A male patient aged 65 years old present with L5/S1 spinal brucellosis. a. lateral view of X-ray showed instability and decreased height of L5/S1 disc; b. sagittal CT images showed lesions involving L5 and S1 vertebral bodies; c. sagittal T1, T2 and fat suppression (stir) images showed inflammatory granuloma formation.

relevant bias, and they were continued recorded to monitor the activity of infection. The visual analogue scale (VAS) and Oswestry Disability Index (ODI) was used to assess the back pain and the pain-related dysfunction. Neurologic deficit and improvement was evaluated using the American Spinal Injury Association (ASIA) scale. The final life functional and quality outcome was graded using functional criteria of Kirkaldy-Willis.

Static and bending digital radiographs were performed to evaluate the progress of fusion and secure of implanted instruments. CT scans were also performed if needed. The achievement of fusion was assessed using the modified radiologic criteria of Lee et al [10]. Segmental sagittal lordotic angle was measured as angle between the upper and lower endplates of the involved vertebral level. The overall lumbar lordotic angel was measured from lower endplate of T12 to upper endplate of S1. The radiographic data was evaluated by two authors independently and recorded as their average value.

2.5. Statistical analyses

The SPSS 17.0 statistical software was used to perform all the statistical analyses. The difference between CRP and ESR value of direct and indirect data before surgery was detected by Mann-Whitney U test. The quantitative data of preoperative and final follow-up were evaluated by Student's *t*-test The rank sum test was used if there was discrepancy in normal distribution. A P value $\leqq 0.05$ was considered to be statistically significant.

3. Results

3.1. Infection status

The titer of standard tube agglutination test for Brucella antibodies was $\geq 1/160$ in all cases while culture of blood or abscess fluid was positive in 10 patients (27.7%). Non-caseating granulomatous

Fig. 2. The tools inside a standard Stimulan® Kit. The powder and fluid could be mixed with antibiotics and stirred into paste for direct injection or producing calcium sulfate beads in 3 different sizes after desiccation in the mold.

Table 2
Infection status and pain-related scores at pre-operation, 4 weeks post-operation and 3 months post-operation.

	VAS	CRP	ESR	ODI
Pre-op	7.5 ± 1.18	31.9 ± 14.3	41 ± 21.8	77.06 ± 9.01
Post-op 4 weeks	3.67 ± 0.95	21.5 ± 17.4	33 ± 22.5	32.44 ± 5.73
Post-op 3 months	2.01 ± 0.82	5.32 ± 2.17	9.87 ± 4.39	10.97 ± 2.74

inflammation was reported as the results of histopathologic examination in all patients. No statistical difference was found in all comparations in ESR and CRP values between direct and indirect recruited groups, even the values of indirect recruited group showed slight increases at 2 days before surgery compared to those at initial diagnosis. Fever was observed in 26 patients (72.3%) pre-operatively. All cases were followed-up for at least 12 months with mean value of 15.6 ± 3.73 months. One patient had delayed wound healing and one patient had superficial would infection respectively, who were both treated successfully by intravenous antibiotic treatment. No clinical or radiological relapses were observed during the follow-up and no revision surgery was needed in all cases.

The average preoperative level of CRP and ESR in all patients were 31.9 ± 14.3 and 41 ± 21.8. Their value declined to 21.5 ± 17.4 and 33 ± 22.5 at 4th week after surgery respectively and returned to normal as 5.32 ± 2.17 and 9.87 ± 4.39 at the 3rd month follow up (Table 2).

3.2. Neurologic status

ASIA Grade D was given to 14 patients with neurologic deficit preoperatively. They all had complete recovery of neurology and returned to ASIA Grade E within 3 months after surgery. The intact of neurologic function remained in all patients until follow-up at 12 months after surgery.

3.3. Radiography evaluation

The segmental lordotic angle was 3.94 ± 9.25° pre-operatively and 9.92 ± 10.82°at 12 months after surgery, with a correction of 5.98 ± 3.54°. The similar correction was also found in the overall lumbar lordotic angel as 6.24 ± 7.93°, which improved from 39.24 ± 8.31°pre-operatively to 45.48 ± 7.28°. The difference was significant ($p < 0.05$) in both segmental and overall lordotic angle between the two time points (Table 3). The $CaSO_4$ beads could be observed in X-ray at 4 weeks follow up. They became unclear at 3 months follow up and were fully absorbed at 12 months post-operatively (Fig.3).According to the modified criteria of Lee, 69% (25/36) of patients reached definitive union at 12 months after surgery while probable union occurred in the rest 31% (11/36) of patients. No detectable gap or movement in the interbody area was found in all patients (Table 4). There was no loosening of implant and no pseudoarthrosis reported that required removal of implants or revision surgery.

Table 3
The data of sagittal lordosis correction from the operation. *:$p < 0.05$ compared to pre-op.

	Segmental lordortic angle	Overall lordortic angle
Pre-op	3.94 ± 9.25°	39.24 ± 8.31°
Post-op	9.92 ± 10.82°*	45.48 ± 7.28°*
Correction	5.98 ± 3.54°	6.24 ± 7.93°

3.4. Functional outcome

The patients reported a mean VAS score of 7.5 ± 1.18 pre-operatively. This value improved to 3.67 ± 0.95 and 2.01 ± 0.82 at week 4 and 12 post-operatively, which indicated an improve rate of 82%. The ODI score improved from 77.06 ± 9.01 pre-operatively to 32.44 ± 5.73at 4weeks post-operatively and further declined to 10.97 ± 2.74 with an overall improvement of 85.8%. The restore of life quality was evaluated based on the Kirkaldy-Willis functional outcome criteria, by which 12 and 20 patients reported excellent and good outcomes while 4 patients reported fair outcomes at 12 months after surgery. The satisfactory rate was 88.9% (Table 4).

4. Discussion

Human brucellosis is a common zoonosis which is reported as a major endemic health problem mainly in the Mediterranean region, in the Middle East and parts of south and central America [11]. However, it has been re-emerging in China since the beginning of the 21 st century with the incidence reaching a historic peak in 2009. Considering the large Chinese population, much more attention should be given to the treatment of human brucellosis in China. The infection mainly affects organs rich in reticulo-endothelial cells, which makes the musculoskeletal system one of the most frequent targets. In earlier reports, the incidence of musculoskeletal infection can reach up to 85% [12,13]. The involvement of spine is more common in the elderly and represents 6–58% of osteo-articular infections [14]. At the beginning of infection, the involvement usually is confined to the anterior portion of superior endplate, which is defined as focal form. As the infection aggravates it may involve the entire vertebral body and diffuse to adjacent interspinal disc and epidural space through ligaments or vascular communications, which is defined as diffuse form. In this study the involvement of brucellosis infection was restricted in one single level in lumbar region in all patients and single-stage TLIF was performed with the $CaSO_4$ drug delivery system to insure the enhanced recovery after surgery

The clinical symptoms of spinal brucellosis are rather non-specific to other types of spondylodiscitis. It may present moderate fever and different degree of spinal pain. Compared to spinal tuberculosis, spinal brucellosis showed a relative less destructive process in the multicenter “Backbone-1” study, with 33% of the patients showed neurologic deficit, spinal instability or deformity [3]. The most affected level in spinal brucellosis is the lumbar spine, followed by thoracic and cervical spine [15]. In this study the involvement of L2–3 and L4-5 account for 38.9% and 33.3% of all cases respectively. This region acts for the most weight-bearing function of the entire spinal column, therefore many cases may develop with progressive back pain and kyphotic deformity. Spinal instability is also a common complication owing to the presence of lumbar lordotic angle. Nevertheless, surgical treatment has been rarely reported for spinal brucellosis compared to the amount of reports on conservative studies. In the current study, we chose surgical treatment because it could thoroughly debride the focus of infection, relieve nerve from compression immediately, restore spinal stability and correct sagittal alignment with lordotic angle. In this study 14 patients with ASIA grade D pre-operatively had complete recovery of neurology and improved to ASIA Grade E within 3 months after surgery. The correction of segmental and overall lordotic angle were 5.98 ± 3.54° and 6.24 ± 7.93° respectively at 12 months follow up, in accordance with other single segment TLIF reports [16]. The correlation between the severity of back pain and the loss of normal lordosis has been proved in earlier studies [17,18]. Thus the surgical procedure could relieve back pain by sufficient debridement of inflammation and correction of lordotic angle, and restore neurologic function from nerve compression. These results contributed to the restore of life quality, with the 57.9% improvement of ODI score and 88.9% satisfactory rate of Kirkaldy-Willis functional outcome criteria.

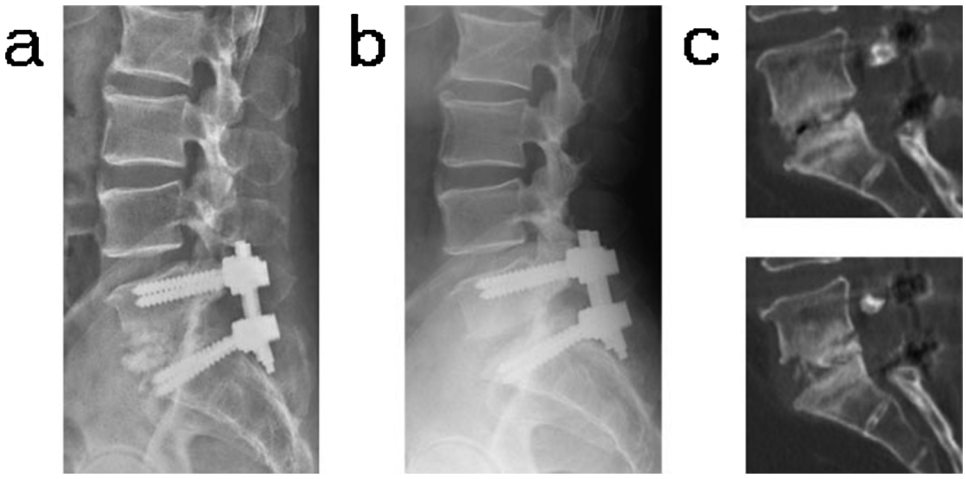

Fig. 3. Post-operative follow-up radiographs of the patients in Fig.1. a. Lateral X-ray at 4 weeks follow-up showed corrected height of L5/S1 disc implanted with intervertebral calcium sulfate and bone grafting; b. lateral X-ray at 12 months follow-up showed absorbed calcium sulfate and interbody fusion; c. sagittal CT images showed satisfied interbody fusion at 12 months follow-up.

Table 4
Results of fusion status and functional outcome and 12 months follow-up.

	Number	Percentage of patients
Fusionstatus		
definitive union	25	69.4
probable union	11	30.6
Kirkaldy-Wills scale		
excellent	12	33.3
good	20	55.6
fair	4	11.1

Posterior approaches, anterior approaches and a combination of both one stage or two stages had all been reported in the treatment of spondylodiscitis and they were frequently compared in literature [19]. Posterior-only approaches are increasingly used in tuberculosis [20] and septic spondylodiscitis of thoracic and lumbar region [21] because the development of transforaminal lumbar interbody fusion (TLIF) surgical technique, which was the decompression and stabilization procedure used in our treatment as one stage operation therapy. This procedure could minimize the traction of nerve root and dura and preserve the function of posterior spinous process ligament complex, avoiding the severe complications in anterior approach and providing a better functional recovery. Some authors questioned that whether TLIF could achieve sufficient debridement and reconstruction of anterior column [22]. But this procedure was proven safe and adequate for spinal brucellosis in our patients and in earlier study [23].The less severe destructive feature of brucellosis might be one of the reasons. Besides, the $CaSO_4$ drug delivery system was also applied in our study to ensure the success of treatment.

There has been controversy regarding the instrument placement in infected area because it might hinder infection clearance after the formation of bacteria biofilm. However, decompression without instrumentation could lead to a reoperation rate as high as 42% in spondylodiscitis, while decompression combine with stabilization had a reoperation rate of 16% [24]. Some authors argued that the implants could be safe because they were placed in the cancellous bone with rich blood flow and the autoimmune system could treat inflammation by preventing bacteria attachment with the influence of antibiotics [36]. In fact we believed the TLIF procedure reported in spinal infection was not perfect, because most reports involved iliac crest harvesting for autologous bone graft. This is because the majority of surgeons still hold the point that the use of cages and bone removed from facets might hinder infection clearance after the formation of bacteria biofilm in spinal infection. For this issue, in this study we introduced the use of a $CaSO_4$ drug delivery system into the surgery treatment for human brucellosis for the first time. These delivery systems have been shown to produce high concentrations at the site of infection and fill dead space after debridement [8]. In earlier in vivo tests, the releasing of antibiotic started immediately after surgery and lasted up to 14 days after implantation [26]. They are especially appropriate when the antibiotic sensitivity has been done to provide effective antibiotic for the delivery system, which is perfect for brucellosis because doxycycline was the first choice in WHO and Ioannina recommendations [4].

In our study, the beads of $CaSO_4$ carrying doxycycline were placed in the anterior half of the debrided interspinal space and around pedicle screws. The radiographic data showed that the absorption of $CaSO_4$ beads was evident at 3 months follow up and fully achieved at 12 months post-operatively. 25 patients achieved definitive fusion with a fusion rate of 69% at the 12 months follow up. All 14 patients with neurologic deficit pre-operatively all had complete recovery of neurology and returned to ASIA Grade E within 3 months after surgery. At the same time no clinical or radiological and clinical relapses were found during the follow-up period. These results proved that $CaSO_4$ drug system was safe to use in spine brucellosis, with no negative impact on the fusion status and neurological function recovery. With these promising results, in future studies we plan to combine the use of such drug delivery system with polyetheretherketone (PEEK) cage in spinal brucellosis, which can avoid autologous iliac bone strut harvesting and further improve functional recovery after surgery.

The improvement of lordotic angle was mainly associated with TLIF procedure and screw-rod fixation and had no direct correlation with the use of $CaSO_4$ system. However, most TLIF for spinal infection used autologous iliac crest as bone graft for fusion. The strength of bone graft will be weakened after infiltration of inflammation, which could result in subsidence of graft material and lead to the loss of lordotic angle in follow-ups. This phenomenon was reported in many researches [18,25]. In this study, the $CaSO_4$ system gave us confidence to restrict fixation on one vertebrae superior and inferior the involved vertebrae and/or disc without any extending to a longer distance in all patients. At final follow up, the maintainess of lordotic angle improvement was satisfactory. Thus we believed that the use of $CaSO_4$ system could reduce the persisted inflammation infiltration to bone graft and help to maintain the improved lordotic angle after TLIF. The restriction of fixation segments also minimized surgical exposure and medical expense of patients, saved innocent motion segments and improved the functional recovery after surgery.

Our study has some limitations. From the current data we could not show the fact that the drug delivery system has an advantage in clearing the spinal brucellosis and improving lordotic angle compared to surgical debridement and fusion alone without the drug delivery system. A prospective randomized controlled study is needed to illustrate these issues. In fact there are reports showed that TLIF alone could achieve satisfactory results in clearing the spinal brucellosis [23]. However, we

believed that the core objective of our work was not to demonstrate that the TLIF combing of $CaSO_4$ drug delivery system was superior to surgical debridement and fusion alone. The main aim of reporting our work was introducing the use of such drug delivery system into spinal infection, because no report was found to focus the use of such system in spine surgery. Our data did prove that this $CaSO_4$ system was safe to use in the interspace without negative impact on fusion rates and neurological function recovery, which could provide confidence for more surgeons to use the system with cages and bones from removed lamina and facets for spinal brucellosis or other infection in future studies. The ultimate goal would be saving iliac crest from harvesting, thus the functional outcomes for the operation therapy could be improved in a great deal.

5. Conclusions

In the current study we reported a surgical procedure combining the use of a $CaSO_4$ drug delivery system in single-stage TLIF for the treatment of spinal brucellosis. Our results demonstrated that this $CaSO_4$ system was safe to use in the operation procedure without negative impact on fusion rates and neurological function recovery. We believed the use of this system would be promising and may be considered as a choice for future treatment in spinal brucellosis or other spondylodiscitis.

Declarations

The authors certify that there are no commercial associations that might pose a conflict of interest in connection with the manuscript. The human protocol for this study has been approved by Shandong University Qilu Hospital (No. KLYY-2014 − 032) and all investigations were conducted in conformity with ethical principles of research. The study was supported by Science Foundation of Qilu Hospital of Shandong University (No. 2017QLQN05).

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