Medical Hypotheses 132 (2019) 109330

Contents lists available at ScienceDirect

Medical Hypotheses

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

# Efficacy of low molecular weight heparin in spinal trauma patients after part concentrated screw surgery and its influence on blood parameters and the incidence of deep venous thrombosis

W. Shiqing*, M. Shengzhong, Z. Cheng, C. Guangqing, G. Chunzheng

*Department of Orthopedics, The Second Hospital of Shandong University, Ji'nan, Shandong Province, China*

ARTICLE INFO

*Keywords:*
Low molecular weight heparin
Part concentrated screw
Pedicle screw surgery
Tissue plasminogen activator
Endothelin

ABSTRACT

This study was to investigate the efficacy of low molecular weight heparin (LMWH) therapy in patients with spinal trauma after part concentrated screw (PCS) pedicle screw surgery (PSS) and its influence on blood parameters and the incidence of deep venous thrombosis. Prospectively, 36 patients with spinal trauma who underwent PSS were randomly divided into an experimental group ($n = 18$) and a control group ($n = 18$). The experimental group was treated with LMWH after the operation. Changes in the vascular endothelial function, inflammatory factors and other blood indexes, and the incidence of deep venous thrombosis in lower extremities were compared between the two groups before and after the surgery. Compared to pre-surgery, the levels of endothelin (ET) and tissue plasminogen activator (tPA) in the experimental group decreased significantly after surgery (all $P < 0.001$), while the levels of ET increased and tPA decreased significantly in the control group (all $P < 0.001$). In addition, compared with pre-surgical levels, interleukin-8 (IL-8), IL-6 and procalcitonin (PCT) decreased significantly in the experimental group after surgery while there was a significant increase in these cytokines in the control group (all $P < 0.001$), with a significant difference in the cytokine levels between the two groups post-surgery ($P < 0.01$). After the surgery, plasma viscosity, erythrocyte electrophoresis time and platelet aggregation rate in the control group were significantly increased from pre-surgery levels (all $P < 0.001$), and these levels were also significantly higher than in the experimental group ($P < 0.01$). The D-dimer (D-D) level in both groups also increased significantly after surgery (all $P < 0.001$), and the level post-surgery was significantly higher in the experimental group as compared to the control group ($P < 0.01$). Finally, the incidence of deep venous thrombosis in the experimental group was significantly lower than in the control group ($P < 0.05$). LMWH is beneficial in reducing the degree of hypercoagulability, hyperviscosity and inflammatory reaction in patients with spinal trauma who underwent PSS. It also effectively reduced the occurrence of deep vein thrombosis in lower limbs after surgery. Thus, it is a candidate for further clinical development.

## Introduction

Spinal trauma has a high incidence rate and is commonly seen in orthopedic clinics. It is often caused by a compression or fracture following a traumatic impact. If not treated appropriately in time, severe spinal trauma can lead to paralysis, which would have a significant impact on patients' physical and mental health as well as the quality of life [1,2]. Because of the complicated anatomical location, clinical treatment of spinal trauma is difficult. In the past, open surgery has been the primary choice of clinical treatment, but the procedure is complicated and highly risky, which made patients' prognosis difficult. Thanks to gradual advances in medical technology, the part concentrated screw (PCS) pedicle screw surgery (PSS) system was developed. It has proved to be a useful and less risky method for the treatment of spinal trauma. This system has good biomechanical properties and a low internal fixation failure rate. However, patients must be confined to absolute bed-rest for an extended period of time after PCS PSS, which leads to an increased incidence of deep venous thrombosis in lower limbs after surgery, and seriously affects patient recovery [3,4]. Previous work has shown that low molecular weight heparin (LMWH) reduces blood viscosity and accelerates blood flow [5]. Till date, most clinical studies have focused on the application of LMWH

* Corresponding author at: Department of Orthopedics, The Second Hospital of Shandong University, No. 247 Beiyuan Street, Ji'nan 250033, Shandong Province, China.

*E-mail address:* wushiqing416@163.com (W. Shiqing).

https://doi.org/10.1016/j.mehy.2019.109330
Received 21 May 2019; Received in revised form 22 July 2019; Accepted 25 July 2019
0306-9877/ 

after resection of malignant tumor and gynecologic surgery, while few studies have evaluated the application of LMWH after PCS PSS, especially with regards to its potential effects on vascular endothelial function.

## Hypothesis

This study is based on the hypothesis that administration of LMWH in patients with spinal trauma, after PCS pedicle screw surgery, is beneficial in reducing hypercoagulability and the inflammatory response in the body.

## Material and methods

### *General data*

Prospectively, 36 patients who were treated for spinal trauma in The Second Hospital of Shandong University from August 2017 to February 2018 were enrolled as participants in this study. A random number table was used to divide the patients into the experimental group (n = 18) and the control group (n = 18). All patients met the diagnostic criteria for spinal trauma according to *Practical Orthopedics* [6]. Inclusion criteria consisted of: Those who (1) met the diagnostic criteria; (2) had PCS PSS indications within 24 h of trauma; (3) with a normal immune system; (4) had no contraindication to the drugs; (5) with spinal cord nerve damage; (6) with complete clinical data; and (7) without serious medical diseases. Exclusion criteria consisted of: Patients (1) with open injury; (2) with severe infection; (3) with malignant tumors; (4) with abnormal coagulation function; (5) with poor compliance; and (6) with immune system diseases. This study was approved by the Medical Ethics Committee of The Second Hospital of Shandong University, and all patients who participated in the study and their families signed the informed consent document.

### *Methods*

All participants enrolled in the study were treated with PCS PSS for spinal trauma. In brief, the patients were kept in a prone position and a posterior median approach was used, following induction of general anesthesia. The upper and lower vertebral laminae and articular processes were fully exposed and localized by imaging fluoroscopy. The pedicle screw was inserted and the bone cortex was thoroughly cleared. The screw was then gradually inserted into the pedicle and into the vertebral body. Finally, the direction and position of the screw was determined using the perspective positioning system, and different types of screws were inserted after tapping and the nuts were locked in place. After the operation, both groups of patients were given antibiotics for 3–5 days to prevent infection. In addition, the experimental group received LMWH (Shenzhen Techdow Pharmaceutical Co., Ltd.), at a dose of 5000 U/time, once a day, for 7 days consecutively.

### *Observation indicators*

The 3 mL fasting venous blood was collected 1 day prior to surgery and 7 days after surgery from subjects in both the groups. The blood samples were centrifuged for 5 min at 3,500 rpm, and the serum was separated and stored at −20 °C for future analysis. The following parameters were evaluated from the serum: (a) Endothelial function was estimated and compared between the two groups by measuring endothelin (ET) and tissue plasminogen activator (tPA) levels. ET was measured by enzyme-linked immunosorbent assay (ELISA) while tPA was measured using chromogenic substrate assay. (b) The serum levels of inflammatory factors such as interleukin-8 (IL-8), IL-6 and procalcitonin (PCT) were measured by ELISA. The ELISA and chromogenic substrate assay were performed according to the manufacturer's instructions (Shanghai Kaliburn Biological Company, China). (c) Hematological parameters, including plasma viscosity, erythrocyte electrophoresis time and platelet aggregation rate, were measured by SA-6000 Automatic Hemorheology Instrument (Beijing Sicceeder Technology Development Co., Ltd., China) and compared between the two groups in samples collected prior to surgery and 7 days after surgery. (d) Coagulation functions, including prothrombin time (PT) and activated partial thromboplastin time (APTT), was measured using a PUN-2048 Series Semi-automatic Coagulation Instrument (Beijing Planet New Technology Co., Ltd., China). The D-dimer (D-D) level was measured by immunoturbidimetry. (e) Lower extremity deep venous thrombosis was screened by Doppler ultrasonography two weeks after the operation.

### *Statistical methods*

Statistical analyses of the data was conducted using SPSS 20.0 software. The measurement data were expressed as mean ± standard deviation($\bar{x}\pm$ sd). A paired t-test was used for intra-group comparison before and after surgery, and an independent t-test was used for comparisons between the two groups. The individual counts were expressed as percentages (%) and compared by $\chi^2$ test. Differences were considered statistically significant when $p < 0.05$.

## Results

### *Comparison of clinical data*

There were no statistically significant differences in the general data of patients in the two groups, including gender, age, mean time course of disease and disease type ($P > 0.05$). This indicates that comparative analysis can be carried out between the two groups (Table 1).

### *Comparison of vascular endothelial function*

There was no significant difference in vascular endothelial function between the two groups before surgery ($P > 0.05$). However, compared to pre-surgical levels, the levels of ET and tPA in the experimental group decreased significantly after surgery (all $P < 0.001$). ET in the control group increased significantly, and tPA decreased significantly (all $P < 0.001$) (Table 2; Fig. 1).

### *Comparison of inflammatory factors*

There was no significant difference in the levels of the inflammatory factors between the two groups before surgery ($P > 0.05$). Compared to pre-surgical levels, IL-8, IL-6 and PCT levels decreased significantly in the experimental group while the factors increased significantly in the control group (all $P < 0.001$). The differences in the inflammatory factors between the two groups after the operation was also significant

**Table 1**
Comparison of clinical data.

| | Experimental group | Control group | $t/\chi^2$ | P |
|---|---|---|---|---|
| Gender | | | 0.111 | 0.739 |
| Male | 10 | 9 | | |
| Female | 8 | 9 | | |
| Age (years) | 37.1 ± 2.3 | 37.1 ± 2.3 | 0.013 | 0.990 |
| Duration of the operation (min) | 204.12 ± 16.05 | 204.25 ± 15.98 | 0.024 | 0.981 |
| The mean course of disease | 13.08 ± 2.01 | 13.14 ± 1.95 | 0.091 | 0.928 |
| Disease type | | | 0.612 | 0.894 |
| Spondylolisthesis | 6 | 7 | | |
| Spinal fracture | 5 | 6 | | |
| Spinal stenosis | 5 | 4 | | |
| Others | 2 | 1 | | |

**Table 2**
Comparison of vascular endothelial function levels ($\bar{x} \pm$ sd)

| | ET (ng/L) | tPA (IU/mL) |
|---|---|---|
| Experimental group (n = 18) | | |
| Before surgery | 25.47 ± 1.56 | 2.89 ± 0.75 |
| After surgery | 16.31 ± 1.20$^{**, \#\#\#}$ | 1.21 ± 0.13$^{**, \#\#\#}$ |
| Control group (n = 18) | | |
| Before surgery | 25.44 ± 1.58 | 2.86 ± 0.69 |
| After surgery | 30.59 ± 1.15$^{\#\#\#}$ | 1.79 ± 0.08$^{\#\#\#}$ |

*Note*: Compared with control group after surgery, $^{**}P < 0.01$; compared within group before surgery, $^{\#\#\#}P < 0.001$. ET, endothelin; tPA, tissue plasminogen activator.

($P < 0.01$) (Table 3).

*Comparison of hematological indexes*

There was no significant difference in any of the hematological indexes between the two groups before surgery ($P > 0.05$). After surgery, the plasma viscosity, erythrocyte electrophoresis time and platelet aggregation rate were significantly increased in the control group (all $P < 0.001$), and were significantly higher than in the experimental group after surgery ($P < 0.01$) (Table 4).

*Comparison of coagulation function*

There was no significant difference in the coagulation function between the two groups prior to surgery ($P > 0.05$). However, compared to pre-surgery, D-D levels in both groups increased significantly after surgery (all $P < 0.001$), and the D-D levels in the experimental group was significantly higher than that in the control group, post-surgery ($P < 0.01$). There were no significant differences in PT and APT between the two groups before and after the operation ($P > 0.05$) (Table 5).

*Comparison of deep venous thrombosis in lower extremities*

One case of lower extremity deep vein thrombosis occurred in the experimental group, for an incidence of 5.56% (1/18). In the control group, however, 7 cases of lower extremity deep vein thrombosis occurred, with an incidence of 38.89% (7/18). The incidence of deep venous thrombosis was significantly lower in the experimental group than in the control group ($P = 0.016$, $\chi^2 = 5.786$). At the same time, after 1 month follow-up, the two groups of patients recovered well, and no re-hospitalization due to hemorrhagic diseases occurred.

**Discussion**

Spinal injuries which mainly include spine fracture, spondylolisthesis, spinal canal stenosis and other types, are usually accompanied by

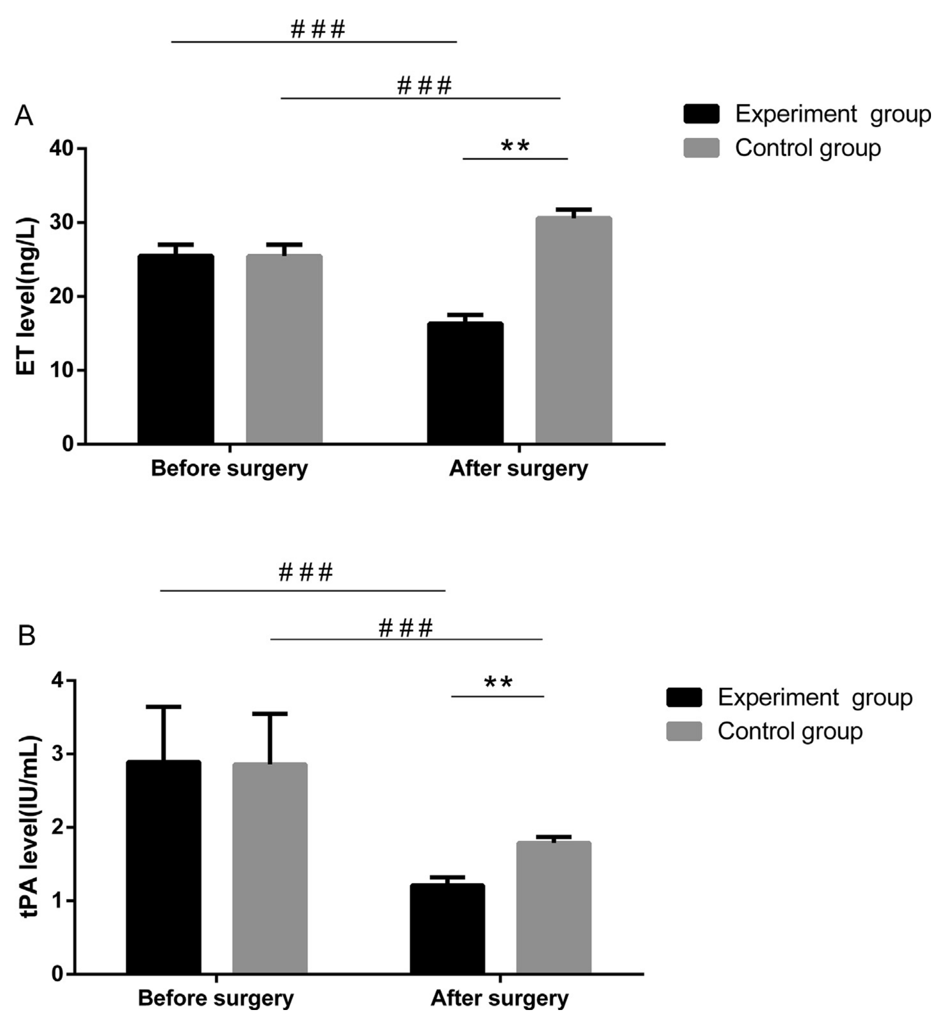


**Fig. 1.** Comparison of vascular endothelial function in both groups. (A) ET level; (B) tPA level. Compared with control group after surgery, $^{**}P < 0.01$; compared within group before surgery, $^{\#\#\#}P < 0.001$. ET, endothelin; tPA, tissue plasminogen activator.

**Table 3**
Comparison of inflammatory factors levels ($\bar{x}\pm$ sd)

| | IL-8 (ng/L) | IL-6 (pg/mL) | PCT (μg/L) |
|---|---|---|---|
| Experimental group (n = 18) | | | |
| Before surgery | 62.97 ± 2.39 | 27.69 ± 8.32 | 1.80 ± 0.27 |
| After surgery | 38.88 ± 5.94$^{**, ###}$ | 9.11 ± 0.95$^{**, ###}$ | 0.63 ± 0.04$^{**, ###}$ |
| Control group (n = 18) | | | |
| Before surgery | 61.76 ± 2.54 | 28.07 ± 8.13 | 1.79 ± 0.28 |
| After surgery | 70.06 ± 3.01$^{###}$ | 33.96 ± 1.88$^{###}$ | 2.98 ± 0.03$^{###}$ |

*Note*: Compared with control group after surgery, $^{**}P < 0.01$; compared within group before surgery, $^{###} P < 0.001$. IL, interleukin.

spinal cord damage [7,8]. According to clinical statistics, the incidence of spinal trauma in China is increasing year by year, with traffic accidents being the primary cause. Due to the physiological and anatomical location of the spine, PCS PSS, which has a higher biomechanical anchoring strength, is widely used in the clinical treatment of spinal injuries [9–11]. It was found that a pedicle screw had a holding force 1.7 times the metal hook and steel wire under the lamina, with a better hardness than the metal hook. This holding force was positively correlated with the diameter of the screw [12,13]. Thus, the PCS PSS operation has proved to be a far better option than traditional open surgery. Nevertheless, spinal surgery is still a significantly longer and invasive procedure due to its complexity. Internal fixation, as performed in PCS PSS, directly leads to the destruction of muscle tissue around the wound due to external traction, resulting in significantly higher platelet reactivity and decreased blood flow speed. Together these factors lead to the formation of deep vein thrombosis of lower extremities.

Many studies have shown that the occurrence and development of deep venous thrombosis in lower extremities after spinal surgery is closely related to factors such as impaired vascular endothelial function, increased blood coagulation, increased blood viscosity, and venous blood flow retardation [14,15]. Among these, endothelial cells are key factors modulating coagulation and thrombosis. ET and tPA are sensitive indicators which reflect vascular endothelial function. ET is a vasoconstrictor released by vascular endothelial cells while tPA, a regulator of fibrinolytic system activity, maintains the dynamic balance of thrombosis/dissolution, and whose level positively correlates with disease severity [16,17]. The present study showed that the levels of ET and tPA after surgery in the experimental group, which received LMWH, were significantly lower than before the operation. However, ET levels in the control group were significantly higher while tPA levels were significantly lower post-surgery. These results suggest that subcutaneous injections of LMWH after PCS PSS can improve the body's vascular endothelial function and facilitate rapid recovery.

Some studies have reported that deep venous thrombosis of lower extremities is a type of acute non-suppurative inflammation, which can release many inflammatory factors as the disease progresses, and can cause coagulation dysfunction [18]. Among them, inflammatory factors like IL-8, IL-6 and PCT are widely responsible. IL-8 is a pro-inflammatory factor produced by monocytes, which can effectively recruit neutrophils and T lymphocytes to the affected tissues, leading to enhanced inflammation, and further damage the vascular endothelial function. IL-6 is also a pro-inflammatory factor with multiple immune regulatory functions and is positively correlated with the degree of inflammation. Prior studies have found that patients with spinal trauma often also present with spinal cord damage, which leads to abnormally increased prothrombin levels and further cause hypercoagulability of the blood [19]. In addition, spinal cord injury can cause abnormal changes in muscle strength and significantly aggravate nerve injury, which can reduce blood pressure and blood flow velocity. Another clinical study has reported that IL-6 could bind to plasminogen activator and abolish its fibrinolytic function, causing rapid platelet aggregation and inducing thrombosis [20]. Animal studies have shown that during a variety of inflammatory reactions, IL-6 can not only seriously damage the vascular endothelial function, but also initiate the coagulation of platelets and increase the APTT and PT levels [21]. As the degree of inflammation becomes more severe, coagulation increases, blood flow becomes slower, and patient prognosis becomes worse.

**Table 5**
Comparison of coagulation function parameters ($\bar{x}\pm$ sd)

| | PT (s) | APTT (s) | D-D (ng/mL) |
|---|---|---|---|
| Experimental group (n = 18) | | | |
| Before surgery | 11.20 ± 1.67 | 35.06 ± 5.17 | 114.67 ± 30.35 |
| After surgery | 11.38 ± 0.38 | 35.13 ± 1.22 | 202.54 ± 30.05$^{**, ###}$ |
| Control group (n = 18) | | | |
| Before surgery | 11.22 ± 1.59 | 35.12 ± 5.08 | 121.68 ± 29.34 |
| After surgery | 11.19 ± 0.21 | 35.27 ± 0.95 | 233.47 ± 35.10$^{###}$ |

*Note*: Compared with control group after surgery, $^{**}P < 0.01$; compared within group before surgery, $^{###}P < 0.001$. PT, prothrombin time; APTT, activated partial thromboplastin time; D-D, D-dimer.

The present study showed that IL-8, IL-6, PCT and D-D levels in the experimental group post-surgery significantly decreased as compared to pre-surgery, and the incidence of deep venous thrombosis was significantly lower in the experimental group than in the control group. After 1 month follow-up, there was no hemorrhagic diseases caused rehospitalization in the two groups. This indicates that LMWH can help to effectively reduce the levels of IL-8, IL-6 and PCT, as well as improve the coagulation function and blood circulation in spinal trauma patients after PCS PSS. This is because LMWH has an activity similar to factor Xa, which can inhibit further increases in plasma viscosity and platelet

**Table 4**
Comparison of hematological index levels ($\bar{x}\pm$ sd)

| | Plasma viscosity (mPa·s) | Erythrocyte electrophoresis time (s) | Platelet aggregation rate (%) |
|---|---|---|---|
| Experimental group (n = 18) | | | |
| Before surgery | 1.37 ± 0.13 | 15.77 ± 1.40 | 48.36 ± 8.85 |
| After surgery | 1.30 ± 0.17$^{**}$ | 15.08 ± 1.46$^{**}$ | 44.06 ± 7.13$^{**}$ |
| Control group (n = 18) | | | |
| Before surgery | 1.35 ± 0.12 | 15.78 ± 1.39 | 48.38 ± 8.90 |
| After surgery | 1.68 ± 0.16$^{###}$ | 18.27 ± 3.32$^{###}$ | 56.48 ± 6.05$^{###}$ |

*Note*: Compared with control group after surgery, $^{**}P < 0.01$; compared within group before surgery, $^{###}P < 0.001$.

aggregation rate, and thus provide a beneficial anti-thrombotic effect. However, LMWH has not been used previously as a routine therapy to prevent deep venous thrombosis in lower extremities after PCS PSS for spinal trauma. Furthermore, LMWH has no definite effect on pulmonary embolism induced by spinal cord injury and thus needs to be further analysed in large-scale and multi-center studies.

In conclusion, LMWH effectively alleviates the hypercoagulability and hyperviscosity of blood and accelerates blood flow in patients with spinal trauma after undergoing PCS PSS. It also lowered the expression levels of inflammatory factors, which is beneficial in reducing the incidence of deep venous thrombosis in lower extremities in patients with spinal injuries.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

This work was supported by the Key Research and Developmental Projects of Shandong Province for Development and application of 3D bio-printing technology based on repair of large bone defects (2016GGX103034).

## References

[1] Coll-Miró M, Francos-Quijorna I, Santos-Nogueira E, et al. Beneficial effects of IL-37 after spinal cord injury in mice. Proc Natl Acad Sci USA 2016;113(5):1411–6.
[2] Yousefifard M, Rahimi-Movaghar V, Nasirinezhad F, et al. Neural stem/progenitor cell transplantation for spinal cord injury treatment; A systematic review and meta-analysis. Neuroscience 2016;322(13):377–97.
[3] Coste CA, Bergeron V, Berkelmans R, et al. Comparison of strategies and performance of functional electrical stimulation cycling in spinal cord injury pilots for competition in the first ever CYBATHLON. Eur J Transl Myol 2017;27(4):7219–21.
[4] Oh SK, Choi KH, Yoo JY, Kim DY, Kim SJ, Jeon SR. A phase III clinical trial showing limited efficacy of autologous mesenchymal stem cell therapy for spinal cord injury. Neurosurgery 2016;78(3):436–47.
[5] Wu X, Xu XM. RhoA/Rho kinase in spinal cord injury. Neural Regen Res 2016;11(1):23–7.
[6] Raspa A, Pugliese R, Maleki M, Gelain F. Recent therapeutic approaches for spinal cord injury. Biotechnol Bioeng 2016;113(2):253–9.
[7] Haque A, Ray SK, Cox A, Banik NL. Neuron specific enolase: a promising therapeutic target in acute spinal cord injury. Metab Brain Dis 2016;31(3):487–95.
[8] Partida E, Mironets E, Hou S, Tom VJ. Cardiovascular dysfunction following spinal cord injury. Neural Regen Res 2016;11:189–94.
[9] Altun I, Yuksel KZ. Ankylosing spondylitis: patterns of spinal injury and treatment outcomes. Asian Spine J 2016;10(4):655–62.
[10] Gungor B, Adiguzel E, Gursel I, Yilmaz B, Gursel M. Intestinal microbiota in patients with spinal cord injury. PLoS One 2016;11(1):e0145878.
[11] Biering-Sørensen F, DeVivo MJ, Charlifue S, et al. International Spinal Cord Injury Core Data Set (version 2.0)-including standardization of reporting. Spinal Cord 2017;55(8):759–64.
[12] Barclay L, McDonald R, Lentin P, Bourke-Taylor H. Facilitators and barriers to social and community participation following spinal cord injury. Aust Occup Ther J 2016;63(1):19–28.
[13] Mahnig S, Landmann G, Stockinger L, Opsommer E. Pain assessment according to the international spinal cord injury pain classification in patients with spinal cord injury referred to a multidisciplinary pain center. Spinal Cord 2016;54(10):809–15.
[14] Kim YH, Ha KY, Kim SI. Spinal cord injury and related clinical trials. Clin Orthop Surg 2017;9(1):1–9.
[15] Zlatev DV, Shem K, Elliott CS. How many spinal cord injury patients can catheterize their own bladder? The epidemiology of upper extremity function as it affects bladder management. Spinal Cord 2016;54(4):287–91.
[16] Knox J. Epidemiology of spinal cord injury without radiographic abnormality in children:a nationwide perspective. J Child Orthop 2016;10(3):255–60.
[17] Brinkhof MWG, Al-Khodairy A, Eriks-Hoogland I, et al. Health conditions in people with spinal cord injury: Contemporary evidence from a population-based community survey in Switzerland. J Rehabil Med 2016;48(2):197–209.
[18] Sunshine JE, Dagal A, Burns SP, et al. Methylprednisolone therapy in acute traumatic spinal cord injury: analysis of a regional spinal cord model systems database. Anaesth Analg 2017;124(4):1200–5.
[19] Piazza M, Schuster J. Timing of surgery after spinal cord injury. Neurosurg Clin N Am 2017;28(1):31–9.
[20] Rouanet C, Reges D, Rocha E, Gagliardi V, Silva GS. Traumatic spinal cord injury:current concepts and treatment update. Arq Neuropsiquiatr 2017;75(6):387–93.
[21] Hosseini SM, Sharafkhah A, Koohi-Hosseinabadi O, Semsar-Kazerooni M. Transplantation of neural stem cells cultured in alginate scaffold for spinal cord injury in rats. Asian Spine J 2016;10(4):611–8.