Perioperative predictors of moderate and severe postoperative pain in idiopathic scoliosis patients following spinal correction and fusion operations

Qingqing Fan, MD[a,d], Han Xie, MD[a], Zhengliang Ma, PhD[b], Zhengxiang Chen, MD[c], Tianhua Yan, PhD[d,*], Weihong Ge, MD[a,*]

Abstract
To investigate the predictive factors of pain intensity during the first 48 hours after spinal correction and fusion operations for idiopathic scoliosis patients.

A total of 290 scoliosis patients who underwent posterior spinal instrumentation and fusion operations were enrolled in this study. A standard surgical and analgesic method was implemented for all participants and pain intensity was evaluated at fixed times within 48 hours after the operation. Variables including demographics (age, sex, body mass index [BMI], patient sources), surgical variables (procedure, duration of operation), intraoperative variables (total transfusion, autologous transfusion, heterogeneous transfusion, fluid intake, use of preventive analgesia) were investigated.

On univariate analysis, BMI, transfusion type and not implementing preventive analgesia were associated with more serious pain after a scoliosis correction operation. Multivariate analysis indicated that receiving heterogeneous transfusion and not implementing preventive analgesia were significant predictive factors for moderate and severe pain after the spinal correction operation.

Our research indicated that the type of transfusion and preventive analgesia were significantly associated with the severity of pain. Body mass and patient sources should be considered before surgery. For patients under high risk of moderate and severe pain, the type of transfusion must be taken into consideration. This study explored the influencing factors of postoperative pain from a novel perspective, but some limitations existed in this present study, and future studies are needed.

Abbreviations: ASA classification = American Society of Anesthesiologists physical status classification, BMI = body mass index, IL-6 = interleukin 6, NRS = Numerical Rating Scale, TNF-α = tumor necrosis factor-α.

Keywords: Idiopathic scoliosis, inflammatory response, postoperative pain, predictor, transfusion

1. Introduction

Scoliosis is a structural, tridimensional deformity of the spine. Characterized by lateral curvature and rotation of the vertebrae with functional limitations and cosmetic problems, idiopathic scoliosis, which accounts for 75% to 80% of all scoliosis,[1–2] is the most common of all types. It has a considerable impact on teenagers' quality of life and imposes a burden on the family and society.[3–4] Surgical treatment is an effective way to correct severe spine deformity when the deformity progressively worsens and cannot be positively corrected by brace treatment.[5]

Spinal correction surgery is one of the most invasive surgical procedures and usually results in moderate to severe levels of postoperative pain. Severe pain may induce implant complications such as construct dislodgement, broken instrumentation, and implant loosening which requires additional revision procedures.[6–7] These conditions adversely affect postoperative outcomes.

In the past several years, pain has become an important indicator for evaluating indicators of outcome and quality of life after surgery.[8] Effective analgesia after surgery could improve patients' prognosis. Therefore, investigating the factors influencing the severity of postoperative pain is crucial to optimizing postoperative pain management and has important clinical implications.

Although numerous studies have focused on the investigation of individual differences in postoperative pain and analgesia effectiveness, the influencing factors of these studies are very limited to particular factors such as incision length and number of fused levels.[9] Based on our experience, scoliosis surgery is associated with massive blood loss during the operation, and many patients accept transfusions. Because transfusion affects inflammatory factors, and the inflammatory reaction is a critical mechanism of acute pain, we hypothesized that aspects of the transfusion may be influencings factor of postoperative pain.

Therefore, we investigated the predictors (including transfusion type) of individual differences in postoperative pain for

[a] Department of Medicine, [b] Department of Anesthesiology, [c] Department of Scoliosis Surgery, The Affiliated Drum Tower Hospital of Nanjing University Medical School, [d] School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu, China.

* Correspondence: Weihong Ge, Tianhua Yan, 210008, Nanjing, 210009 (e-mail: 6221230@sina.com, yth0001@126.com).

idiopathic scoliosis patients who underwent spinal correction operations. In addition, we investigated other important factors that may influence pain intensity, such as social and psychological factors, by referring to other research.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board of Drum Tower Hospital. Idiopathic scoliosis patients who received spinal correction surgery at Drum Tower Hospital from January 2014 to October 2017 were reviewed. Patients who met the following eligibility criteria were included: diagnosis of idiopathic scoliosis and accepted posterior route spinal correction surgery. All participants were Han Chinese.

Patients with these conditions were excluded:

(1) surgery with growth instrumentation other than pedicular screws (growth instrumentation placement or extension),
(2) a prior operation,
(3) a revision operation, or
(4) lost data. (Fig. 1)

Demographic information was collected, including sex, age, body mass index (BMI, calculated by dividing weight in kilograms by corrected height in meters squared) and American Society of Anesthesiologists physical status (ASA) classification.

2.2. Perioperative anesthesia and surgical procedure

All the variables investigated were from patients anesthetized by the same team of anesthetists and operated on by the same team of surgeons. Total intravenous anesthesia and posterior spinal correction surgery were applied to all patients.

Anesthesia information: All patients who underwent surgery received total intravenous anesthesia. No premedication was administered. The venous infusion pathway was established after patients arrived in the operating room. Anesthesia was induced with midazolam (0.1 mg/kg), etomidate (0.2 mg/kg), cisatracurium besylate (0.4 mg/kg) and sufentanil (0.4 μg/kg). Anesthesia was maintained with propofol at a target blood concentration of 4~6 μ
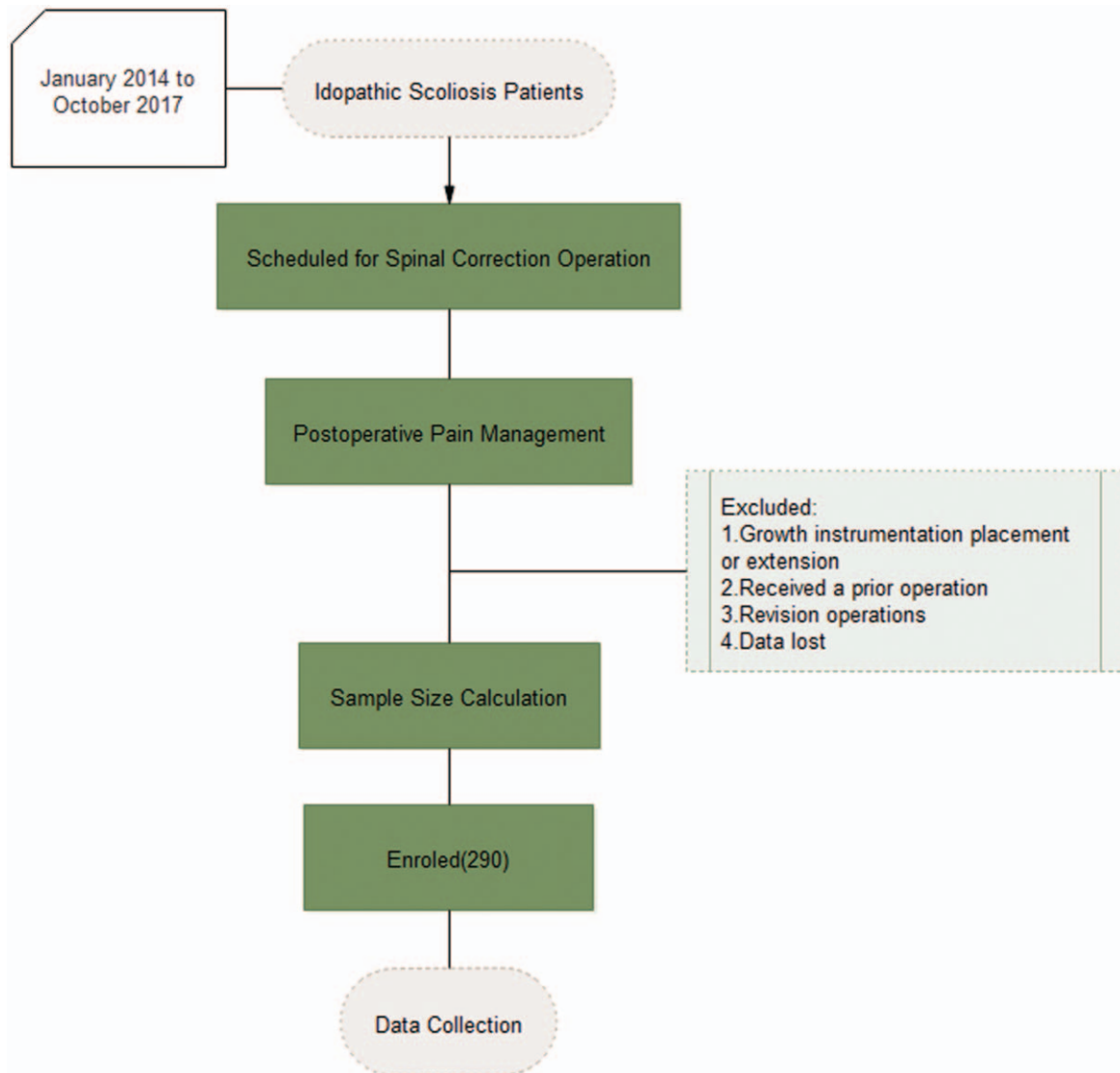
Figure 1. Research flowchart. 290 patients were totally enrolled in this study.

g/mL using a target-controlled infusion (TCI) pump; patient-controlled intravenous analgesia was provided after surgery.

All patients had posterior arthrodesis of the spine with instrumentation and application of bone grafting and fusion. A dissection was performed to expose the bilateral facet. Screw placement was performed in the scheduled vertebral body. In addition, facet osteotomies were completed after screw placement based on the surgeon's judgment. The bilateral pre-contoured rod was bent beforehand and then placed to correct the curvature. In situ bending and segmental derotational maneuvers were then performed where appropriate. The wound surface was douched and effective hemostasis was performed before bone-grafting into the vertebral plate. In addition, a drainage tube was placed in layers for all patients, before incision closure. Intravenous (IV) flurbiprofen axetil (100 mg) was used as preventive analgesia depending on the anesthesiologists' choice.

Intraoperative fluid intake (colloids or crystalloids), total volume of transfusion through the operation (autologous transfusion included volumes of homologous blood received during the operation, and heterogeneous transfusion included red blood cell and fresh frozen plasma), and duration of operation were recorded.

2.3. Postoperative analgesia

Patients accepted the standard postoperative analgesic plan after the operation. Patient-controlled intravenous analgesia was provided 5 minutes before the end of the operation and established with continuous fentanyl (adult: 15~20 µg/kg, children: 0.3~0.8 µg/kg) infusion and dexamethasone 10 mg and ondansetron 8 mg diluted in normal saline in a total volume of 100 mL. Dexamethasone and ondansetron were used to prevent nausea/vomiting because of a high incidence of vomiting with fentanyl in young females. PCA was programmed for delivery with a continuous infusion background speed of 2 mL/h and a bolus dose of 0.5 mL, with a 15-minute lockout, for breakthrough pain when the pain rating score was above 3/10. PCA bolus times were recorded to assess the intensity of pain. Intravenous (IV) flurbiprofen axetil 100 mg b.i.d. was used as a combined analgesic to relieve inflammation. If the patient complained of unbearable pain, IV pethidine was administered as a rescue analgesic as required.

2.4. Pain intensity measurement

Pain condition was monitored during hospitalization. The measurement was assessed by the postoperative pain management guidelines formulated by the American Pain Society, and the postoperative pain management guidelines formulated by the Chinese Society of Anesthesiology.

Pain measurements were assessed at multiple time points every day immediately after the operation and continued after postoperative day 2 by follow-up assessment. Pain intensity was measured by the numerical rating scale (NRS). Intensity scores ranged from 0 to 10, where 0 indicated no pain and 10 indicated the most pain. A score of 1 to 3 was defined as mild pain, and 4 to 10 was defined as severe pain. The trapezoidal method was used to calculate the AUC for pain for the first 48 hours after surgery (AUC 48) with pain scores collected at fixed time points. The most intensive pain rating for each independent day was assessed and recorded. Times of vomiting after the operations were recorded during the follow-up period. All administered work was accomplished by the same postoperative pain management team consisting of trained pharmacists.

2.5. Statistics analysis

To estimate the group size, we used the following standard formula: $n = \{Z_{1-a/2}[P(1-P)/B]^{1/2} + Z_{1-b}[P1(1-P1) + P2(1-P2)(1-B)/B]^{1/2}\}^2/[P1+P2]^2(1-B)]$, based on the previous study intended to investigate predictors for scoliosis correction surgery.[10–11] The calculation results showed that the number of patients was at least 138 in each group, considering a dropout rate of 5%; 290 patients were analyzed in this study.

Statistical analysis was performed using IBM SPSS Statistics software (version 22.0; SPSS Inc., Chicago, IL). Continuous variables were presented as the mean ± SD or median and quartiles (25th, 75th). Categorical variables were expressed as percentages.

To assess the relevant factors of the patient, univariate analyses were performed with Student t test or Mann–Whitney U test where appropriate, depending on the data distribution characteristics. Categorical variables were analyzed using the chi-squared test.

To identify the risk factors predicting moderate and severe pain, multiple linear regression was used for multivariate analysis. Multivariate regression models were performed to obtain the final regression model of AUC 48. The significance level was defined as 0.05.

3. Results

3.1. Descriptives

In total, 290 cases were analyzed. Descriptive statistics for the patient characteristics are presented in Table 1. The mean patient age was 15.45 ± 3.70 years old and 255 of the patients (87.9%) were female. A total of 85 (29.3%) patients suffered moderate or severe pain (NRS>3). A total of 184 (63.4%) patients received spinal instrumentation and fusion only and 106 (36.6%) had an osteotomy procedure. For all patients, the overall mean AUC 48 of NRS was a pain score of 85.08 ± 36.09.

3.2. Trends of postoperative pain and analgesia effect

Among the 290 patients who underwent scoliosis correction surgery, 84 (28%) patients had bolus dosages within 48 hours, and 25 (8.6%) patients had boluses more than 4 times. Postoperative vomiting (POV) occurred in 62 (21.3%) patients. Details of the pain condition are shown in Table 2. Changes in the average pain score at fixed time points during the 48 hours after the operation are presented in Figure 2.

3.3. Univariate analysis

Our study evaluated pain intensity at multiple time points per day through postoperative day 2. According to the univariate analysis results, (Table 3), BMI, transfusion (autologous transfusion and heterogeneous transfusion separately), and not implementing preventive analgesia were associated with more serious pain after a scoliosis correction operation. In addition, there was a difference in the patient sources between the 2 groups, but this difference did not reach statistical significance. We used these variables in the multivariate analysis.

3.4. Multivariate analysis

To identify the risk factors of moderate and severe pain, multiple linear regression was used to investigate the variables that showed a significant difference ($P < .1$) in the univariate analysis.

Table 1
Patient characteristics.

Variables	Results (n = 290)	Mild pain (NRS ≤ 3)	Moderate and severe pain (NRS > 3)
Sex, n (%)			
Female	255 (87.9%)	181 (88.3%)	74 (87.1%)
Male	35 (12.1%)	24 (11.7%)	11 (12.9%)
Age, years	15.45 ± 3.70	15.22 ± 3.56	16 ± 4
BMI, kg/m^2	19.42 ± 2.78	19.32 ± 2.94	19.67 ± 2.36
ASA, n (%)			
I	7 (2.4%)	3 (1.5%)	4 (4.7%)
II	252 (86.9%)	181 (88.2%)	71 (83.5%)
III	31 (10.7%)	21 (10.2%)	10 (11.8%)
Patients' Sources, n (%)			
Urban	153 (52.8%)	114 (55.6%)	39 (45.9%)
Rural	137 (47.2%)	91 (44.4)	46 (54.1%)
Duration of Operation, minutes	237.18 ± 52.33	236.72 ± 49.97	238.29 ± 57.93
Procedures			
Spinal Instrumentation and Fusion, n (%)	184 (63.4%)	131 (63.9%)	53 (62.4%)
Combined Osteotomy, n (%)	106 (36.6%)	74 (36.1%)	32 (37.6%)
Blood Lost, mL	537.50 (300,831.25)	500 (300,800)	700 (400,1075)
Preventive Analgesia			
Flurbiprofen Axetil (100mg)			
No Preventive Analgesia	170 (58.6%)	130 (63.4%)	40 (47.1%)
	120 (41.4%)	75 (36.6%)	45 (52.9%)
Transfusion			
Total, mL	637.50 (400,931.25)	600 (400,900)	800 (500,1175)
Autologous Transfusion, mL	162.5 (0,375)	125 (0,370)	250 (0,400)
Heterogeneous Transfusion, mL	400 (300,600)	400 (300,600)	600 (300,837.5)
Intraoperative Fluid Intakes			
Colloids, mL	1000 (1000,1500)	1000 (1000,1500)	1000 (1000,1500)
Crystalloids, mL	1500 (1000,2000)	1500 (1000,2000)	1500 (1000,2000)
Maximal Pain Score (NRS)	3.66 ± 1.54		
AUC48 (NRS)	82.92 ± 38.89		

Variables are shown as mean ± SD, median with median (25th, 75th) when appropriate.
ASA Classification = American Society of Anesthesiologists physical status, BMI = body mass index, NRS = Numerical Rating Scale.

In addition, patient sources were taken into the investigation as social and psychological factors have a huge impact on pain. The results of multivariate regression demonstrated that receiving a heterogeneous transfusion and not implementing preventive analgesia were significant predictive factors for moderate and severe pain after spinal correction operation. (Table 4) BMI, receiving an autologous transfusion and patient sources lost statistical significance in the multivariate analysis.

4. Discussion

Spinal correction and fusion is an invasive procedure with a considerable risk of postoperative acute pain. The identification of predictive factors for postoperative pain could optimize postoperative pain control. Identifying the predictors of moderate and severe pain after scoliosis correction operations are

Table 2
Pain condition within 48 hours after operation.

Pain Condition	Incidence (percentage)
PCA Bolus Times	0: 206 (71.0%)
	1–3: 59 (19.4%)
	4 above: 25 (8.6%)
POV Times	0: 228 (78.6%)
	1–3: 54 (18.6%)
	4 above: 8 (2.7%)

PCA = patient controlled analgesia, POV = postoperative vomiting.

crucial to optimizing postoperative pain control, promoting the effect of the treatment, and improving patients' experiences. Previous studies have focused on surgery type and length of the incision. Factors that may influence inflammatory reactions were neglected and social and psychological factors were confirmed to be associated with pain.
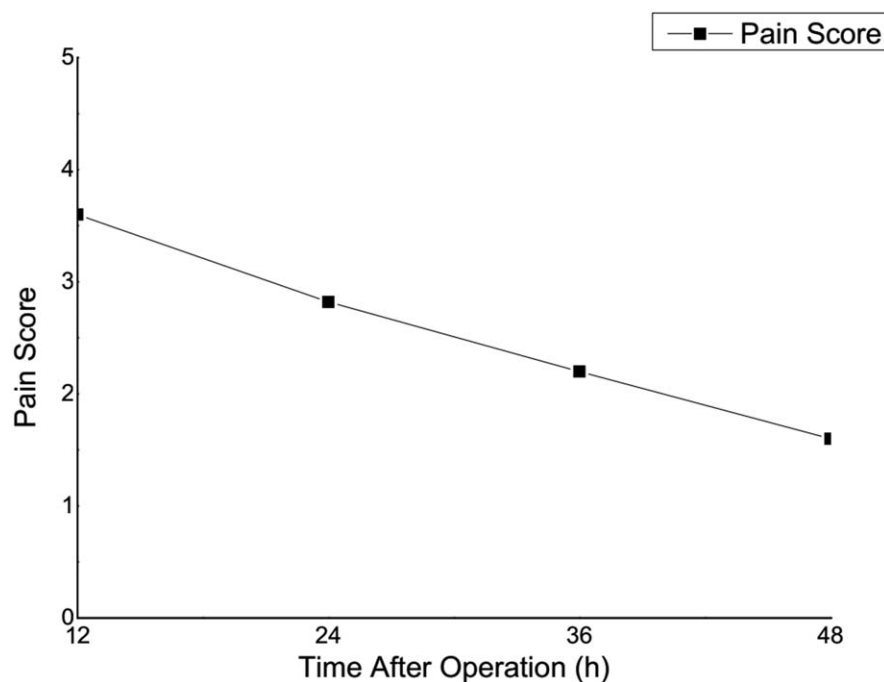
Our work investigated whether the demographic and perioperative variables tested in this research predicted a difference in postoperative pain during the initial 48 hours for patients under posterior scoliosis correction and fusion operations. Univariate analysis showed that BMI, transfusion (including autologous and heterogeneous transfusion), and not implementing preventive analgesia were influencing factors of postoperative pain. In addition, patient sources may have impacted the severity of pain, but not reach statistical significance. According to the multiple linear regression, only receiving a heterogeneous transfusion and not implementing preventive analgesia were predictive.

Contrary to previous findings found by Kim et al,[12] demographic variables (age, sex) and surgical variables (surgery type) were not an influencing factor of postoperative moderate and severe pain, which was consistent with previous findings. Connelly et al[10] found that pain did not have a direct correlation with the severity of scoliosis or surgical differences. Compared with demographic and scoliosis factors, preoperative pain and psychological factors-modified individual differences in postoperative pain trajectory, indicating that psychological factors play an important role in the mechanism of pain. We found that the

Figure 2. Pain score (average) within 48 hours after operation. The change of pain score (NRS) with time after operation. NRS=Numerical Rating Scale.

patient source is an influencing factor of moderate and severe pain, and our results further confirm the view above.

We found that BMI correlates with moderate and severe pain (P=.027) after the operation. It has been observed that obese patients often complain of severe pain. Jun Hozumi,[13] et al found that resistin, a kind of adipokine that is a cytokine that resides in adipose tissue, can modulate inflammatory processes, which is bidirectionally related to an increase in nonspecific proinflammatory cytokines. Macrophages in adipose tissue are activated after tissue inflammation and secrete more proinflammatory cytokines, such as resistin, which can further aggravate the inflammatory response of the tissue. The relationship between adipose tissue and inflammation provides theoretical support for our funding. The relationship between body mass and the distribution of fat should be considered in future studies.

In addition, we observed that transfusion had a significant difference in patients between the mild and moderate-severe pain groups. These results indicated that the transfusion was correlated with the severity of pain. Our results showed that receiving a heterogeneous transfusion is an influencing factor of moderate and severe pain compared with autologous transfusion. This finding indicated that the type of transfusion is associated with individual differences in postoperative pain and analgesia effects. Prior studies generally confirmed that the inflammatory reaction plays a crucial role in the mechanism of acute pain after an operation, and increased inflammatory factors such as interleukins and tumor necrosis factor-α (TNF-α) were crucial factors in the inflammatory reaction.[10] Activation of inflammation during transfusion is closely related to the severity of postoperative pain. The inflammatory response can be achieved through high expression of inflammatory mediators such as TNF-a and interleukin 6 (IL-6). TNF-a and IL-6 have significant proinflammatory activity, which can mediate both tissue damage and inflammatory cascade activation.[14–15]

Many studies have shown that differences exist in the expression of inflammatory cytokines between autologous and homogeneous transfusions. Qu et al[16] found that both the levels of TNF-a and IL-6 and cytokines, named sCD40L and CINC,

Table 3

Univariate analysis of predictive factors for severe pain within 48 hours after scoliosis correction operation.

Factors	P value
Sex	.769
Age	.102
BMI	.027*
Patients' Sources	.131
Duration of Operation	.852
Procedures	.803
Transfusion	
Total	.004*
Autologous Transfusion	.040*
Heterogeneous Transfusion	.018*
Intraoperative Fluid Intakes	
Colloids	.116
Crystalloids	.674
Preventive Analgesia	.010*

BMI=body mass index.
* P<.05.

Table 4

Multivariate analysis of predictive factors for severe pain within 48 hours after scoliosis correction operation.

Factors	B	Std. Error	Beta	95% CI	P value
Constant	15.721	17.385			
BMI	1.087	0.780	0.078	−0.447–2.622	.164
Autologous Transfusion	0.007	0.009	0.044	−0.011–0.024	.440
Heterogeneous Transfusion	0.017	0.006	0.162	0.005–0.028	.005*
Patients' Sources	4.287	4.452	0.264	−4.328–12.902	.328
Preventive Analgesia	20.792	4.377	0.055	12.029–29.555	.000*

BMI=body mass index.
* P<.05.

which play a role in the chemotaxis of inflammatory cells in inflammatory processes in the autologous transfusion group, were significantly higher than in the heterogeneous transfusion group, indicating that autologous transfusion had an inhibitory effect on the inflammatory response and that the secretion of inflammatory cytokines is less than that of heterogeneous transfusion. The results of previous studies provide theoretical support for our hypothesis.

Activated inflammatory cytokines are suspected to be associated with individual differences in postoperative pain and analgesia that were effective after scoliosis surgery. Therefore, we hypothesized that the intensity of pain after the operation was correlated with the type of transfusion during the operation. Heterogeneous transfusion induced the expression of inflammatory cytokines, and elevated inflammatory cytokines are suspected to be associated with individual differences in postoperative pain and analgesia effects after scoliosis surgery. However, earlier research has found the opposite. High levels of plasma IL-6 expression were found after autologous transfusion in research by Schroeder et al[17] Whether the type of transfusion impacts the inflammatory response remains to be examined.

Furthermore, according to our results, receiving preventive analgesia was a protective factor against postoperative pain, and this is consistent with the idea of multimodal analgesia. Preventive analgesics are recommended for better control of postoperative pain.

There are several limitations to this present study. First, we did not determine levels of inflammatory factors such as IL-6 and TNF-a. Therefore, the levels of inflammatory factors could not compared between the different pain intensity groups. In addition, postoperative pain was influenced by genetic polymorphisms which are associated with the pharmacokinetics and pharmacodynamics of analgesics.[18] We did not investigate how genetic factors impacted the analgesic effect.

Uncontrolled postoperative pain is a considerable complication following spinal correction surgery. According to our results, the type of transfusion and preventive analgesia were significantly associated with the severity of pain. Body mass and patient sources should be considered before surgery. For patients under high risk of moderate and severe pain, the type of transfusion must be taken into consideration. The identification of these predictors may be useful for making adequate preparations for severe acute pain after the operation and reducing the severity of pain with an appropriate analgesia plan. The goal is to optimize postoperative pain management and manage the patients' subjective experience. There are several limitations in this present study. Consequently, further study is needed to verify our results. More research is needed to identify individual differences in the influencing factors of postoperative pain severity and analgesia effects.

Acknowledgments

Author contributions

Conceptualization: Weihong Ge.
Project administration: Tianhua Yan.
Visualization: Zhengliang Ma, Zhengxiang Chen.
Writing – original draft: Qingqing Fan.
Writing – review & editing: Han Xie.

References

[1] Adobor RD, Rimeslatten S, Steen H, et al. School screening and point prevalence of adolescent idiopathic scoliosis in 4000 Norwegian children aged 12 years. Scoliosis 2011;6:23.

[2] Wong HK, Hui JH, Rajan U, et al. Idiopathic scoliosis in Singapore schoolchildren: a prevalence study 15 years into the screening program. Spine (Phila Pa 1976) 2005;30:1188–96.

[3] Pellise F, Vila-Casademunt A, Ferrer M, et al. Impact on health related quality of life of adult spinal deformity (ASD) compared with other chronic conditions. Eur Spine J 2015;241:3–11.

[4] Waldrop R, Cheng J, Devin C, et al. The burden of spinal disorders in the elderly. Neurosurgery 2015;77(Suppl 4):S46–50.

[5] Rose PS, Lenke LG. Classification of operative adolescent idiopathic scoliosis: treatment guidelines. Orthop Clin North Am 2007;38:521–9.

[6] de Kleuver M, Lewis SJ, Germscheid NM, et al. Optimal surgical care for adolescent idiopathic scoliosis: an international consensus. Eur Spine J 2014;23:2603–18.

[7] Reames DL, Smith JS, Fu KM, et al. Complications in the surgical treatment of 19,360 cases of pediatric scoliosis: a review of the Scoliosis Research Society Morbidity and Mortality database. Spine (Phila Pa 1976) 2011;3618:1484–91.

[8] Wong GT, Yuen VM, Chow BF, et al. Persistent pain in patients following scoliosis surgery. Eur Spine J 2007;16:1551–6.

[9] Landman Z, Oswald T, Sanders J, et al. Prevalence and predictors of pain in surgical treatment of adolescent idiopathic scoliosis. Spine 2011;36: 825–9.

[10] Connelly M, Fulmer RD, Prohaska J, et al. Predictors of postoperative pain trajectories in adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 2014;39:E174–81.

[11] Milbrandt TA, Singhal M, Minter C, et al. A comparison of three methods of pain control for posterior spinal fusions in adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 2009;34:1499–503.

[12] Kim SY, Jung SW, Choe JW, et al. Predictive factors for pain after endoscopic resection of gastric tumors. Dig Dis Sci 2016;61:3560–4.

[13] Hozumi J, Sumitani M, Nishizawa D, et al. Resistin is a novel marker for postoperative pain intensity. Anesth Analg 2018.

[14] Thomas L, Rao Z, Gerstmeier J, et al. Selective upregulation of TNFalpha expression in classically-activated human monocyte-derived macrophages (M1) through pharmacological interference with V-ATPase. Biochem Pharmacol 2017;130:71–82.

[15] El-Rasheidy FH, Essa ES, Mahmoud AA, et al. Elevated serum adiponectin is related to elevated serum ferritin and interleukin-6 in beta-thalassaemia major children. J Pediatr Endocrinol Metab 2016;29:953–8.

[16] Jing-lei QU, Yuan-zheng YANG. Influence of intraoperative autotransfusion and allogeneic transfusion on coagulation function, immune function and inflammatory factors in patients with cardiac surgery. J North Sichuan Med Coll 2018;33:192–5.

[17] Schroeder S, von Spiegel T, Stuber F, et al. Interleukin-6 enhancement after direct autologous retransfusion of shed thoracic blood does not influence haemodynamic stability following coronary artery bypass grafting. Thorac Cardiovasc Surg 2007;552:68–72.

[18] Ren ZY, Xu XQ, Bao YP, et al. The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: a systematic review and meta-analysis. Pain Physician 2015;18:131–52.