FACTORS AFFECTING THE FORMATION OF BONE BLOCK IN PATIENTS WITH ISTHMIC SPONDYLOLISTHESIS

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Objective. To analyze significance of the influence of various factors on the fusion rate in patients with isthmic spondylolisthesis.
Material and Methods. A retrospective monocenter study included data from 41 patients aged 18 years and older with isthmic spondylolisthesis who underwent transforaminal interbody fusion with cage using a four-screw rigid transpedicular fixation system. The influence of potential risk factors on the fusion rate was studied.
Results. A univariate analysis showed that obesity ($p = 0.037$) and the use of non-steroidal anti-inflammatory drugs (NSAIDs) for more than three months ($p = 0.007$) significantly affect the formation of a bone block. When compiling a logistic regression model, it was found that a combination of obesity, smoking, and the use of NSAIDs for more than three months significantly worsens the prognosis of bone block formation ($p = 0.007$; $R2N = 0.405$; $AUC = 0.850$).
Conclusion. The study showed that the absence of bone block formation in patients with isthmic spondylolisthesis may be associated with smoking, obesity, and the use of NSAIDs for more than three months. Keeping these factors in mind and trying to minimize their presence can help ensure better radiographic outcomes after surgery.
Key Words: isthmic spondylolisthesis, fusion rate, radiologic outcome, risk factors.
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Isthmic spondylolisthesis is the displacement of the superjacent vertebra body relative to the subjacent one owing to the presence of pars interarticularis defect [1]. The progression of the disease and clinical manifestations are associated with instability of the spinal motion segment, accelerated intervertebral disc degeneration, and foraminal stenosis at this level [2, 3]. Conservative management is the first step to improving the quality of life of patients with symptomatic isthmic spondylolisthesis. Nowadays, various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, physiotherapy, and physical therapy are successfully used. Nevertheless, if multimodal conservative management is ineffective, surgical intervention is indicated. Today, the surgery of isthmic spondylolisthesis includes decompression, interbody fusion, and fixation of the affected segment [4, 5]. The bone block formation at the surgery level is one of the main factors for the successful treatment outcome. The literature describes many factors capable of influencing the bone block formation. Nevertheless, there is no consensus among researchers to date.

The objective is to analyze the significance of the influence of various factors on the bone block formation in patients with isthmic spondylolisthesis.

Material and Methods

Patients

A retrospective monocentric cohort study included data from 41 patients with isthmic spondylolisthesis operated on in 2015–2020.

Inclusion criteria:

1) 18 y.o. and older;

2) isthmic spondylolisthesis confirmed by instrumental methods of diagnosis;

3) isthmic spondylolisthesis of a single vertebra;

4) absence of indications for surgical treatment at other segments;

5) availability of previous results of instrumental methods of diagnosis;

6) a minimum 12-month prospective follow-up after surgical treatment.

Exclusion criteria:

1) prior surgery for spinal pathology;

2) spondylolysis of other segments;

3) scoliosis of more than 10° according to Cobb;

4) a severe concomitant somatic pathology.

The average age of the patients was 48.8 ± 13.6 years. In 39 (95.1 %) patients, displacement of the L5 vertebra was noted, in 2 (4.9 %) – of the L4 vertebra. The degree of displacement was assessed based on to X-ray data according to the Meyerding classification: the 1st degree – 16 (39.0 %) patients, the 2nd – 23 (56.1 %), the 3rd – 2 (4.9 %) patients.

Methods

During surgical treatment, the patients underwent the amelioration of compression of nerve structures by bilateral decompression of spinal cord roots through a monolateral approach using a surgical microscope. After decompression at the approach side, transforaminal interbody fusion with a cage was

performed. The fixation was performed with four transpedicular screws. The vertebra repositioning was performed by unforced reduction on a fixed rod through a pre-inserted polyetheretherketone (PEEK) cage.

The following factors affecting the bone block formation were evaluated: gender, age, obesity, smoking, long-term use of NSAIDs, the amount of residual displacement of the vertebra after surgery, the interbody height after surgery, bone density, the filling index of the vertebral body and pedicles with transpedicular screw.

The bone block formation was assessed according to CT findings 12 months after surgery on the Christensen scale [6]. The first degree was characterized by the presence of bony bridges between the vertebral bodies, occupying more than 30 % of the area of the endplates; the second degree – by that less than 30 %; the third degree – by the absence of bony bridges without signs of bone rarefaction; the fourth degree – by the absence of bone bridges and signs of bone rarefaction; and the fifth degree – by pseudoarthrosis (cystic cavities, marginal bone rarefaction around the fixation system and interbody implant).

Data on gender, age, height, and weight were collected by analyzing medical records. Obesity was considered a condition in which the body mass index (BMI) exceeded 30. The duration of NSAIDs use was analyzed after 12 months of follow-up. If the administration was more than 3 months, it was considered to be chronic. The amount of residual displacement was detected based on the control X-ray findings.

An interbody height was measured at three points on the sagittal section on CT scans after surgery: along the front edge of the endplates, at the back edge, and in the center between the endplates. The average between these values was regarded as the interbody height value [7].

Bone density was evaluated using preoperative CT images. On the sections in the axial projection, Hounsfield units were evaluated at the level of pedicles, as well as in the lower quarter of the superjacent vertebral body and in the upper quarter of the subjacent vertebrae, using software averaging by the slice. The average value was accepted as a reflection of the patient's bone density (Fig. 1) [8].

The filling index of the vertebral pedicles with transpedicular screws and the relative length of the screw in the vertebral body indicate the number of trabeculae around the screw. These values were calculated using postoperative CT images. The relative length of the screw was estimated as a percentage of the length of the inserted screw to the maximum possible length in axial images (Fig. 2). The filling index of the pedicle was calculated using the method of Otsuki et al. [9]. The method is to measure the diameters of the vertebral pedicle and the inserted screw with further differencing of the squares of these values (Fig. 3).

The analysis of the influence of factors was performed in two groups of patients, identified by a bone block formation. Group 1 included 33 patients with the first and second degrees of severity of bone block according to Christensen when bone bridges form between the vertebral bodies. Group 2 comprised of 8 patients with the third, fourth, and fifth degrees. This type of severity is manifested in the absence of bone bridges between the vertebral bodies.

Statistical analysis

Statistical data processing was performed using Jamovi software version 1.8. $P < 0.05$ was considered as the statistical significance level.

To identify the normality of the distribution of quantitative indicators, we relied on the Shapiro – Wilk test, as well as on graphical data representations. All quantitative data in the study were subject to the normal distribution law. The Student's t-test was used for indicators of age, percentage of reduction, residual displacement of the vertebra, the value of the interbody space, Hounsfield units, and the filling indices of the body and pedicle. The 2 criterion was used in the analysis of qualitative indicators (gender, obesity, smoking, and duration of NSAIDs for more than three months).

Moreover, a prognostic model was developed to determine the probability of the bone block formation depending on groups of factors by binary logistic regression. The variance of a favorable outcome was evaluated under Nagelkerke's coefficient of determination.

Results

A bone block was formed in 80.48 % of patients a year after surgery. Group 1 (Christensen A1, A2) comprised 33 patients (11 men, 22 women) aged 48.5 ± 14.2; Group 2 (Christensen A3, A4, A5) was of 8 (5 men, 3 women) aged 48.9 ± 11.1. Outcome analysis depending on gender did not reveal a statistically significant difference ($p = 0.129$). The age difference between the compared groups also appeared to be statistically insignificant ($p = 0.943$). The number of patients with obesity in Group 1 was 8 (24.2 %); in Group 2 – 5 (62.5 %). Statistical analysis confirmed the significance of this factor ($p = 0.037$). Six patients (18.2 %) were smokers in Group 1; 4 (50.0 %) patients in Group 2. Despite the superior ratio of smoking patients to non-smokers in Group 2 (compared to the Group 1), the difference was statistically insignificant ($p = 0.060$). The studied bone density by defining the number of Hounsfield units in Group 1 averaged 304.135 ± 133.896 HU; in Group 2 – 344.613 ± 141.166 HU. No statistically significant difference could be identified ($p = 0.452$). Among patients with a formed bone block, 8 (24.2 %) consumed NSAIDs for more than three months after surgery, and among those with an unformed bone block – 6 (75.0 %). The difference in these indicators was statistically significant ($p = 0.007$; Table 1).

The study of factors associated with surgery did not reveal statistically significant differences between the groups. For example, the average residual displacement in Group 1 was 3.74 ± 3.08 mm; in Group 2 – 4.14 ± 3.73 mm (despite the difference in absolute numbers, the difference was statistically insignificant; $p = 0.753$). The interbody height in Group 1 averaged 7.90 ± 1.68 mm and in Group 2 – 9.39 ± 3.73 mm ($p = 0.095$). The relative screw length in Group 1 averaged 90.94 ± 5.27%; in the

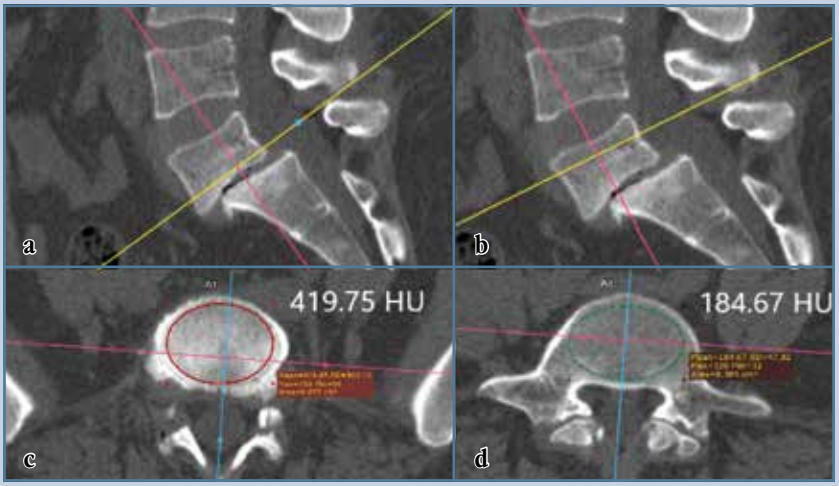

Fig. 1
The study of bone density by measuring Hounsfield units (HU): **a, c** – the levels of slices on the sagittal plane; **b, d** – the selection of the area for measuring the number of Hounsfield units

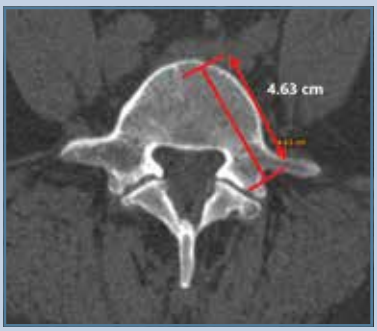

Fig. 2
Measurement of the relative transpedicular screw length

Group 2 – 90.99 ± 2.78 % (p = 0.980). The filling index of the vertebral pedicle with a screw in Group 1 averaged 0.493 ± 0.281; in Group 2 – 0.611 ± 0.269 (p = 0.287). The measurement results are given in Table 2.

A statistically significant difference in the groups of patients with formed and unformed bone blocks was found when analyzing the number of patients using NSAIDs for a long time after surgery, as well as obesity in patients. This indicates the influence of these factors on bone block formation. Nevertheless, the study results indicate the absence of significant influence of age, residual displacement, smoking, interbody height, the filling indices of the body and pedicles, as well as the bone density index on the bone block formation in patients with isthmic spondylolisthesis.

Considering the data obtained by binary logistic regression, two prognostic models were developed to identify the probability of bone block formation. In one case, it depended on statistically significant factors – the presence of obesity and the use of NSAIDs for more than three months (F1); in another case – bearing in mind also the smoking of patients (F2). Both prognostic models were statistically significant (p = 0.015 and p = 0.007, respectively). The Akaike information criterion (AIC) for the first model was 38.1; for the second one – 36.5; the Bayesian information criterion (BIC) for both models was 43.3. According to the value of Nagelkerke's coefficient of determination, the first model explains 29.4 % and the second one – 40.5 % of the observed variance of the bone block formation in patients with isthmic spondylolisthesis. ROC curves for both models were also constructed; the areas under the curves (AUC) were calculated. It was 0.801 for the first model and 0.850 for the second one. Data comparison of two prognostic models revealed that, despite the statistical insignificance of smoking as a factor affecting bone block formation, a combination of factors (smoking, the use of NSAIDs for more than three months, obesity) increased the risk of an unfavorable outcome in patients (Table 3).

Discussion

In the course of the study, we tried to identify the main factors impacting bone block formation in patients with isthmic

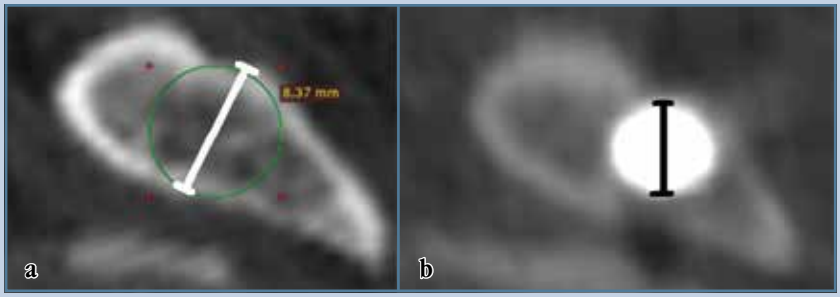

Fig. 3
Measurement of the filling index of the pedicle with a screw on the coronary plane: **a** – calculation of the minimum pedicle size; **b** – measurement of the diameter of the used transpedicular screw

spondylolisthesis. According to the data obtained, a large role is given to chronic administration of NSAIDs, obesity, and smoking.

Comparing these results with the literature data, attention is drawn to the inconsistency of information regarding the influence of various factors presented in many papers on this issue.

It has been repeatedly demonstrated that age, as well as the bone density often associated with it, have a serious effect on bone block formation [10]. Nevertheless, when analyzing a sample of patients with isthmic spondylolisthesis, the following conclusion can be reached. Considering the age peculiarities and the lack of significant somatic pathology in the majority of patients, this factor is not as essential as in the group of patients with degenerative spondylolisthesis.

Many papers have considered the influence of gender. For example, Christensen et al. [6] have shown that women have less potential for bone block formation. This is confirmed by other papers, especially related to bone density and based on this increased risk of pseudoarthrosis [10-12]. Meanwhile, in other studies, the influence of gender has not been proven, as in our study [13, 14]. This can be partly explained by the hormonal peculiarities of older women and the frequent postmenopausal osteoporosis, which is unusual for our sample.

One of the most controversial factors considered in the world literature is the use of NSAIDs in the postoperative period and their effect on bone block formation. Since the beginning of the 2000s, numerous studies, including experimental ones, have been performed. Some papers report the undoubted effect of drugs on bone block formation [15, 16]. In others, on the contrary, researchers declare the absence of their effect on osteogenesis [17, 18]. There is data on the dose-response effect of NSAIDs. In this regard, some authors note that analgesic therapy in the postoperative period is progressively performed with the use of opioid drugs [19]. We used a time interval of 3 months after surgery as an indicator of the duration of NSAIDs administration. The analysis of our sample revealed the undoubted influence of chronic administration on bone block formation.

Obesity is another factor that is not related to surgery but is often studied in world sources. Several papers [20, 21] have shown the effect of obesity on pseudoarthrosis, various perioperative complications, and the risk of reoperations. However, Kalb et al. [22] deny the effect of obesity on bone block formation. We have confirmed the statistical significance of this factor in our study.

Smoking may be associated with an increased risk of pseudoarthrosis [13, 15]. It was impossible to identify statistical significance in the conducted study with univariate analysis. Nevertheless, in constructing a model that includes smoking, administration of NSAIDs, and obesity, the influence of addiction as a co-factor has been demonstrated. It significantly reduces the rate of bone block formation.

Risk factors associated with surgery have been repeatedly considered in various studies. The transpedicular system parameters, cage height, as well as the volume of reduction, are often called significant for bone block formation [9, 13, 23, 24]. The conducted study and statistical analysis do not enable us to suggest the significance of the interbody height, residual displacement, and the parameters of the inserted transpedicular screws on the radiological outcome 12 months after surgery in patients with isthmic spondylolisthesis.

Limitations of the study

Our study has certain limitations. Firstly, it is a retrospective monocentric observation. Secondly, it is essential to consider the small sample size. It is impossible to study the quality of the prepared endplates during the surgical treatment. This factor is vital for bone block formation. To improve the evidence level is required to conduct a multicenter prospective study with many patients.

Conclusions

The retrospective study identified statistically significant factors affecting bone block formation in patients with isthmic spondylolisthesis. Both the doctor

Table 1
Demographic profiles and factors unrelated to surgery

Factor	Group 1	Group 2	p value
Gender, n	11 M; 22 F	5 M; 3 F	0.129
Age, y.o.	48.5 ± 14.2	48.9 ± 11.1	0.943
Obesity, n (%)	8 (24.2)	5 (62.5)	0.037
Smoking, n (%)	6 (18.2)	4 (50.0)	0.060
Chronic administration of NSAIDs, n (%)	8 (24.2)	6 (75.0)	0.007

Table 2
Radiological measurements

Value	Formed bone block	Lack of bone block	p value
Bone density, HU	304.135 ± 133.896	344.613 ± 141.166	0.452
Average residual displacement, mm	3.74 ± 3.08	4.14 ± 3.73	0.753
Interbody height after surgery, mm	7.90 ± 1.68	9.39 ± 3.73	0.095
A relative screw length in the vertebral body, %	90.94 ± 5.27	90.99 ± 2.78	0.980
Filling index of the pedicle with screw	0.493 ± 0.281	0.611 ± 0.269	0.287

and the patient need to understand the increased risk of complications, including the onset of pseudoarthrosis in certain groups of patients. Considering the high probability of an unfavorable outcome in the group of patients using NSAIDs for more than three months, patients with obesity, as well as smokers, it is imperative to set a task aimed at reducing the number of these modifiable risk factors.

The study had no sponsors. The authors declare that they have no conflict of interest.

Table 3

Comparison of predictive models compiled by binary logistic regression

Model	p value	AIC	BIC	R^2N	AUC
F_1	0.015	38.1	43.3	0.294	0.801
F_2	0.007	36.5	43.3	0.405	0.850

F_1 — obesity in the patient and the use of NSAIDs for more than three months after surgery,
F_2 — smokers with obesity and the use of NSAIDs for more than three months after surgery.

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