Distribution of Pathogenic Bacteria of Postoperative Wound Infection and Early Prediction Value of Serum in Children with Hypospadias

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ABSTRACT

The objective of this study was to investigate the distribution of pathogens and the early predictive value of serum in children with hypospadias. The sample consisted children with hypospadias between January 2019 and December 2021 at the Second Affiliated Hospital. 136 children were treated with operation and one-stage urethral reconstruction and divided into infection group (n=18) and non-infection group (n=118). The multivariate logistic regression analysis showed that Snodgrass, penile downward curve, scrotal dysplasia, prolonged operation time, C-reactive protein (CRP), soluble myeloid triggered receptor 1 (sTREM-1), soluble intercellular adhesion molecule-1 (sICAM-1), white blood cell (WBC) and neutrophil / lymphocyte ratio (NLR) at 24 h after operation were the risk factors for postoperative wound infection in children with hypospadias (P<0.05). ROC curve analysis showed that the ROC-AUC predicted by CRP, sTREM-1, sICAM-1, WBC and NLR at 24 h after operation were 0.729, 0.788, 0.821, 0.833, 0.765 and 0.802 respectively. The ROC-AUC of the combination of the above infection indexes was 0.904. The main wound infection after hypospadias is gram-negative bacteria infection. Snodgrass, penile curvature, scrotal dysplasia, prolonged operation time and more than 24 h after operation can increase the risk of wound infection in children with hypospadias. The combination of the above infection indexes has important value in predicting wound infection, and more attention should be paid to the children with the above risk factors in clinical nursing.

INTRODUCTION

Clinical hypospadias can be characterized by varying degrees of downward bending of the penis and micturition spray, and some children may be accompanied by scrotal or testicular dysplasia, which not only affects the normal micturition and reproductive function, but also causes psychological trauma (He *et al.*, 2022). At present, surgical treatment is the only option for hypospadias. In order to achieve better results, one-stage urethral reconstruction is often performed. Although there are many surgical methods at present, none of them has been widely recognized in clinic, among which postoperative wound infection is a clinical problem in the application of various surgical methods. In this study, the pathogens and risk factors of wound infection after hypospadias were analyzed. In addition, early prediction of postoperative wound infection in children, in order to give the corresponding intervention measures in advance, is of great significance to reduce postoperative wound infection. C-reactive protein (CRP) is a commonly used index of inflammatory response in clinic, which can be significantly increased in the early stage of inflammatory response and has high sensitivity (Masson-Lecomte *et al.*, 2014). Soluble myeloid trigger receptor 1 (sTREM-1) is a kind of immunoglobulin that participates in the triggering and mediating process of inflammatory response, so it can be increased in the early stage of bacterial infection (Sanz Codina and Zeitlinger, 2022). Soluble intercellular adhesion molecule-1 (sICAM-1) belongs to the immunoglobulin superfamily, which can promote the expansion of inflammation in the early stage of inflammation through

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adhesion (Judlin and Thiebaugeorges, 2009). Studies have found that the neutrophil/ lymphocyte ratio (NLR) is related to the inflammatory response of the body, and its change is earlier than the increase of leukocytes (Liu *et al.*, 2017). The above-mentioned indexes can be increased in the early stage of inflammatory reaction, but there are few studies on predicting wound infection. Therefore, this study further analyzed the predictive value of CRP, sTREM-1, sICAM-1, WBC and NLR in the early stage of wound infection after hypospadias operation.

MATERIALS AND METHODS

Subjects

The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (WMU) is a provincial grade A comprehensive hospital of Zhejiang, which also serves as the Second School of Clinical Medicine affiliated to WMU. The sample for this retrospective study consisted of 136 children with hypospadias diagnosed at the hospital between January 2019 and December 2021, aged from 6 months to 12 years old, with an average age of 2.24±0.48 years. Inclusion criteria: clinical manifestations of downward curvature of penis, micturition spray, etc., physical examination confirmed the diagnosis of hypospadias, primary urethral reconstruction, complete clinical data, voluntary participation and signed informed consent. Exclusion criteria were antibiotic users 2 weeks before operation, penile curvature > 30°, other malformations such as hermaphroditism, patients with severe hepatorenal cardiopulmonary insufficiency, mental disorders and incomplete clinical data.

Experimental design

According to the postoperative wound infection, the patients were divided into infection and non-infection groups. Diagnosis of wound infection (Berrios-Torres *et al.*, 2017): Performance for fever, fatigue, anorexia; persistent sharp pain at the incision site, with bloody, purulent or serous exudation, throbbing pain after suppuration, purulent fluid after ulceration. Physical examination can find that the incision exudation increases, the skin color of the infection turns red, local skin temperature increases and tenderness is obvious, lumps can be found in the early stage, wave sensation can be touched in the later stage of abscess formation, pus can be extracted by puncture, and pathogenic bacteria can be found by bacterial culture (Karst and Van Hecke, 2012).

Basic information

Basic information was recorded in detail, including age, body mass index (BMI), type of hypospadias (penile body type, coronal groove type, penile scrotal type), operation method (Snodgrass, Magpi, Koyanagi, Mathieu, Onlay), whether with penile curvature, scrotal or testicular dysplasia, etc. Perioperative indicators: including operation time, intraoperative blood loss, hospital stay and so on.

Infection index

C-reactive protein (CRP) was detected by immunofluorescence dry quantitative method before, 24 h and 72 h after operation. Serum sTREM-1 and sICAM-1 levels were detected by enzyme linked immunosorbent assay (ELISA). Blood cell analysis instrument was used to detect white blood cell (WBC), neutrophils and lymphocytes, and calculate NLR.

Microbiological examination

The incisional exudates of all patients in the infection group were collected under aseptic conditions, and the pathogens were analyzed by Siemens WalkAway-96Plus automatic microbiological identification and drug sensitivity analyzer. *Klebsiella pneumoniae* ATCC-700603 was used as quality control standard while *Escherichia coli* ATCC25922 was used as negative control.

Statistical analysis

SPSS23.0 software package was used to deal with the experimental data. The measurement data with normal distribution and uniform variance are expressed by (±s) and t-test, while the counting data are expressed by percentage (%) and corrected by χ^2 test. If n is less than 40, t is less than 1 or less than 5 is greater than 1, Fisher exact probability method is adopted. Analysis of variance was used for comparison among groups, and LSD-t test was used for comparison between the two groups. The analysis of influencing factors was multi-factor unconditional Logistic regression, and the step-back method was used to select and eliminate variables. ROC curve was used to analyze and predict the value. The difference was statistically significant (P<0.05).

RESULTS

Among the 136 children with hypospadias, 18 cases had wound infection after operation, with an incidence of 13.23%, of which 4 cases occurred within 72 h while the rest occurred 72 h after operation. 118 children had no wound infection after operation, accounting for 86.77%. A total of 26 strains of pathogenic bacteria were detected in 18 samples, 16 strains of Gram-negative bacteria (61.54%), of which *Escherichia coli* was the most, 9 strains of Gram-positive bacteria (34.62%), of which *Enterococcus faecalis* was the most, and 1 strain of fungus

(3.85%) was *Candida albicans.* The operation time and hospital stay in the infection group were longer than those in the non-infection group (P<0.05) (Table I).

Table I. Comparison of intraoperative and postoperative conditions between the two groups (m±s).

Group	Operation time (min)	Intraoperative bleeding volume (ml)	Hospitalization time (d)
Infection (n=18)	89.16±11.25	30.02±7.41	10.61±2.52
Non-infected (n=88)	78.11±10.21	28.18±7.62	8.48±2.09
t	3.015	4.324	3.712
P	0.000	0.000	0.000

Table II shows the level of CRP, sTREM-1, sICAM-1, WBC and NLR before operation, at 24 h and 72 h after operation in infected group compared to non-infected group. All these values were raised after operation than those before operation (P<0.05). CRP, WBC and NLR at 72 h after operation were raised than those at 24 h after operation (P<0.05). sTREM-1 and sICAM-1 at 72 h after operation were reduced than those at 24 h after operation (P<0.05). CRP and WBC at 24 h after operation in non-infection group were raised than those before operation and decreased to preoperative level at 72 h after operation

(P<0.05). There was no difference in CRP, sTREM-1, sICAM-1, WBC and NLR between the two groups before operation, but CRP, sTREM-1, sICAM-1, WBC and NLR in infection group 24 h and 72 h after operation were raised than those in non-infection group (P < 0.05) (Table II).

Table III shows the logistic regression analysis of multiple factors affecting postoperative wound infection in children with hypospadias showed that Snodgrass operation, penile curvature, scrotal dysplasia, prolonged operation time, postoperative 24 h CRP, sTREM-1, sICAM-1, WBC and NLR were risk factors for postoperative wound infection in children with hypospadias (P<0.05) (Table III).

Table IV shows the results of predictive value of different infection indexes on postoperative wound infection in children with hypospadias showed considering that there is a strong collinear relationship between each index data and each time point, and some of the children's wound infection occurred within 72 h after operation, the infection index of 24 h after operation was selected to further analyze and predict the value. The ROC-AUC predicted by the above infection indexes were 0.729 (0.638-0.818), 0.788 (0.706-0.876), 0.821 (0.790-0.852), 0.833 (0.749-0.923), 0.765 (0.672-0.856), 0.802 (0.712-0.902), respectively. The ROC-AUC of the combination of the above infection indexes was 0.904 (0.824-0.983).

Table II. Comparison of infection indexes at different time points (m±s).

Time (h) after operation	CRP (mg/L)		sTREM-1 (ng/L)		sICAM-1 (ng/ml)		WBC (*109/L)		NLR	
	Infection group (n=26)	Non-infected group (n=118)	Infection group (n=26)	Non-infected group (n=118)	Infection group (n=26)	Non-infected group (n=118)	Infection group (n=26)	Non-infected group (n=118)	Infection group (n=26)	Non-infected group (n=118)
0h	5.02±1.12	5.09±1.31	5.36±1.38	5.14±1.17	145.36±10.38	138.44±11.27	6.86±1.38	6.84±1.27	1.55±0.31	1.53±0.21
24 h	15.39±2.34*#	10.12±1.34#	20.78±3.32*#	5.16±1.08	313.58±21.32*#	140.16±12.38	13.18±2.52*#	10.16±2.38#	2.18±0.36*#	1.56±0.32
72h	22.37±5.12*#γ	5.15±1.23γ	14.06±2.41*#γ	5.14±1.02	174.06±11.41*#γ	136.06±11.02	16.86±2.41*#γ	6.86±1.32γ	3.41±0.51*#γ	1.56±0.25
Between groups										
F	32.643	23.786	55.678	42.845	17.453	32.643	23.786	55.678	42.845	17.453
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Time										
F	67.434	15.977	68.485	155.473	382.234	67.434	15.977	68.485	155.473	382.234
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Interaction										
F	14.598	6.784	11.697	16.045	12.534	14.598	6.784	11.697	16.045	12.534
P	0.000	0.021	0.000	0.000	0.000	0.000	0.021	0.000	0.000	0.000

*, Compared with the non-infected group at the same time (P<0.05); #, Compared with that before operation (P<0.05); γ, Compared with 1 day after operation (P<0.05).
CRP, C-reactive protein; sTREM-1, soluble myeloid trigger receptor 1; sICAM-1, soluble intercellular adhesion molecule-1, WBC, white blood cell; NLR, neutrophil / lymphocyte ratio.

Table III. Logistic regression analysis of multiple factors affecting postoperative wound infection in children with hypospadias.

Factors	Regression coefficient	Standard error	Wald	P	OR	OR 95% confidence interval
Snodgrass	0.976	0.449	4.728	0.030	2.654	1.101 -6.398
Downward curvature of penis	1.183	0.557	4.507	0.034	3.264	1.095 -9.729
Scrotal dysplasia	1.423	0.288	24.420	0.000	4.150	2.360 -7.298
Operation time	0.860	0.319	7.260	0.007	2.362	1.264 -4.414
24 h after operation						
CRP	1.308	0.169	59.645	0.000	3.697	2.653 -5.152
sTREM-1	1.153	0.498	5.364	0.021	3.169	1.194 -8.411
sICAM-1	0.113	0.068	2.767	0.096	1.120	0.980 -1.280
WBC	1.180	0.411	8.265	0.004	3.256	1.456 -7.281
NLR	1.632	0.165	97.540	0.000	5.112	3.698 -7.067
Constant term	0.711	0.356	7.445	0.000	-	-

Table IV. Predictive value of different indexes for postoperative wound infection in children with hypospadias.

Factors	AUC (0.95CI)	Sensitivity	Specificity	Yoden index	Truncation value
Operation time	0.729(0.638~0.818)	0.793	0.661	0.457	81.23min
24 h after operation					
CRP	0.788(0.706~0.876)	0.851	0.735	0.587	13.98mg/L
sTREM-1	0.821(0.790~0.852)	0.888	0.769	0.647	13.14 ng/L
sICAM-1	0.833(0.749~0.923)	0.900	0.768	0.662	186.36ng/ml
WBC	0.765(0.672~0.856)	0.834	0.702	0.536	$12.78*10^9$/L
NLR	0.802(0.712~0.902)	0.852	0.755	0.603	1.88
Joint application	0.904(0.824~0.983)	0.933	0.865	0.773	-

DISCUSSION

Hypospadias is one of the common congenital malformations of the urinary system in children. It is reported that there is one hypospadias in every 125-300 newborns. At present, the cause of hypospadias is not clear, genetic, environmental and other factors may be involved in the occurrence of hypospadias, but in recent years, studies have reported that the incidence of hypospadias is on the rise (El-Karamany *et al*., 2017). The older the operation age of hypospadias is, the greater the risk of psychosocial and sexual function problems is. Therefore, it is suggested that surgical treatment should be carried out as early as possible, and the best operation time is 6-12 months after birth (Ceccarelli *et al*., 2021). At present, there are more than 300 surgical methods for hypospadias, but any kind of operation is affected by postoperative complications, among which wound infection is one of the common postoperative complications. In this study, 136 children with hypospadias were analyzed and found that 18 children had wound infection after operation, with an incidence of 13.23%, most of which occurred 72 h after operation.

Bacterial culture is an important index to guide the use of antibiotics in postoperative pulmonary infection, but its positive rate is low and because bacterial culture takes time, it is of low value in the early use of antibiotics to guide postoperative wound infection (Dokter *et al*., 2020). At present, with the change of objective environment and the unreasonable use of subjective antibiotics, the distribution and drug resistance of pathogens have changed, so understanding the distribution and drug resistance of pathogens is of great value to the early use of antibiotics. In this study, it was found that Escherichia coli was the most common pathogen of wound infection, followed by Enterococcus faecalis in Gram-positive bacteria. It is consistent with the results of pathogens of urological wound infection reported (Liu *et al*., 2022). Therefore, in clinical practice, we can refer to the distribution of the above-mentioned pathogens and give corresponding antibiotics to control the disease in the early stage.

Clinical understanding of the risk factors of a

disease can give the necessary intervention in advance in order to reduce the risk or severity of the disease. This study found that Snodgrass, penile curvature, scrotal dysplasia, prolonged operation time, and increased levels of 24 h CRP, sTREM-1, sICAM-1, WBC and NLR after operation can increase the risk of wound infection in children with hypospadias. Another study also found that age > 2 years old, mode of operation, penile curvature and scrotal dysplasia were independent risk factors for postoperative complications in children with hypospadias (Yu *et al*., 2022). In this study, no correlation was found between age and wound infection, but may be related to different postoperative observation indicators. This study analyzed postoperative complications including urinary fistula, urethral stricture and so on. The urethral orifice after Snodgrass's operation is closer to the normal appearance and easy to operate, so it is the mainstream surgical method for hypospadias at present. However, because the anastomosis is in the middle position, some children may increase the risk of wound infection because of urinary fistula. For children with penile curvature and scrotal dysplasia, the urethral development is poor, and the difficulty of operation increases. The longer the reconstructed urethra is, the higher the incision suture tension is, and the operation time is prolonged. And it will seriously affect the postoperative blood flow and increase the risk of wound infection (Irene *et al*., 2021). STREM-1 is expressed on innate immune cells and plays an important role in the initiation and development of various inflammatory reactions such as infection by binding to glycoprotein ligands, and can reflect the severity of infection (Mumingjiang *et al*., 2014). SICAM-1 is also a pro-inflammatory adhesion factor, which participates in the early inflammatory response mainly through adhesion and promotes with a variety of infectious inflammatory factors such as interleukin-6 (Liu *et al*., 2017). CRP is one of the most commonly used markers of inflammatory response in clinic, and it can be significantly increased in the early stage of inflammation. Neutrophils are inflammatory activating factors and lymphocytes are inflammatory regulatory factors. the balance between neutrophils and lymphocytes has been destroyed in the early stage of inflammatory response (Cocorocchio *et al*., 2020), therefore, NLR can better reflect the early infection of the body.

At present, there is no objective index for early prediction of wound infection. In this study, the risk factors affecting postoperative infection of hypospadias were predicted and analyzed. It was found that 24 h CRP and WBC alone had low predictive value. The analysis showed that CRP was one of the markers of infection and had high sensitivity in the early stage of infection, but its specificity was low due to stress. White blood cell is also one of the

reference indicators of infection, but its rise has a certain lag, and is also affected by the stress response of the body (Yu *et al*., 2020). Although the ROC-AUC of sTREM-1, sICAM-1 and NLR levels at 24 h after operation was more than 0.8, the value of combined prediction was higher, with a ROC-AUC of 0.904, a sensitivity of 93.3% and a specificity of 86.5%. Therefore, it is suggested that the combined prediction of multiple indexes can be carried out in clinic.

CONCLUSION

The present study shows that postoperative wound infection in hypospadias is mainly caused by gram-negative bacteria, Snodgrass, penile curvature, scrotal dysplasia, prolonged operation time and more than 24 h after operation can increase the risk of postoperative wound infection in children with hypospadias, and the combination of the above infection indexes is of great value in predicting wound infection. attention should be paid to the children with the above risk factors in clinical nursing.

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