Risk factors for obstructive complications after endoscopic correction of vesico-ureteral reflux using polyacrylate polyalcohol copolymer

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Abstract
Use of polyacrylate-polyalcohol copolymer (PPC) after endoscopic correction (EC) of vesico-ureteral reflux (VUR) is highly effective but is associated with a higher risk of obstructive complications (OC) compared with other implants. We undertook a STROBE compliant retrospective investigation and studied the OC risk factors to increase the practical safety of PPC.

Overall, 798 patients (464 [58.1%] girls and 334 [41.9%] boys) from 5 hospitals in whom PPC was routinely used were evaluated retrospectively. The patients were subdivided into 2 groups. Group I consisted of 754 (94.5%) children (449 [59.5%] girls and 305 [40.5%] boys) without OC. Median age was 41 months [Q1: 18.0; Q3: 81.0]. Group II comprised 44 (5.5%) patients (29 [65.9%] boys and 15 [34.1%] girls) experiencing OC, and their median age was 21.5 months [Q1: 12.0; Q3: 43.0]. Clinical and renal ultrasound examinations were carried out 1 day and 1 month after EC, and then every 6 months after EC. At the follow-up examination approximately 6 months after EC, voiding cystourethrography (VCUG) was performed. All patients with OC underwent diuretic renography.

OC occurred in 44 (5.5%) of 798 children, in some cases as late as 60 months after endoscopic injection of the bulking agent PPC for correction of VUR. Univariate analysis revealed that higher age (P = .001), higher grade of VUR (P < .001), male gender (P < .001), second injection (P = .003), and EC injection using hydrodistension implantation technique (HIT; P < .001) represented significant risk factors. At multivariate analysis, only male gender (P = .0078), higher grade of VUR (P = .0044), HIT technique (P < .0001), and second injection (P = .04) represented significant risk factors for the occurrence of OC.

We identified young age, male gender, high reflux grade, HIT technique, and second endoscopic injections as factors associated with the risk of OC after EC of VUR using PPC as a bulking agent. Thus, patients who have undergone EC with PPC must be monitored sonographically for occurrence of OC for at least 60 months after the intervention.

Abbreviations: AUC = area under the curve, DMSA = dimercaptoposuccinic acid, EC = endoscopic correction, HIT = hydrodistension implantation technique, IRSC = International Reflux Study Committee, OC = obstructive complications, OR = odds ratio, PPC = polyacrylate-polyalcohol copolymer, ROC = receiver operating characteristic, RU = renal units, STING = subureteral transurethral injection, UTI = urinary tract infection, UVJO = uretero-vesical junction obstruction, VUCG = voiding cystourethrography, VUR = vesico-ureteral reflux.

Keywords: endoscopic correction, hydrodistension implantation technique, obstruction, polyacrylate polyalcohol copolymer, subureteral transurethral injection, uretero-vesical junction, vesico-ureteral reflux

1. Introduction
Endoscopic correction (EC) of vesico-ureteral reflux (VUR) was introduced by Matoušek[1] in the early 1980s. Although EC has a lower success rate than ureteral re-implantation in the correction of VUR, it has become widely popular due to its safety and minimally invasive character. Uretero-vesical junction obstruction (UVJO) is a rare complication of EC to treat VUR in children, occurring in less than 1% of patients.[2-3]

Success rates of EC range from 59.2% to 85.0%,[4-6] reflecting the recent development of new bulking agents and injection
technologies. The newly engineered substances were hoped to ensure better EC effectiveness without adverse influence on the safety of the endo-urologic intervention.

The favorable safety of EC using the subureteral transurethral injection (STING) technique triggered the development of the hydrodistension implantation technique (HIT) and “Double HIT” injection technique of the bulking agent. These advanced methods resulted in an increased EC success rate. Initial reports of polyacrylate-polyalcohol copolymer (PPC) application appeared in 2010. The authors reported better effectiveness when using PPC, with success rates of EC ranging from 83.6% to 92.7%.[9,10] However, routine use of PPC in practice demonstrated a higher risk of uretero-vesical junction obstruction (UVJO).[11,12] These increased frequencies of UVJO triggered our interest in the factors affecting the risk of UVJO development. Thus, we retrospectively assessed the frequency and time course of UVJO development associated with the use of PPC during EC and aimed to identify the risk factors involved.

2. Materials and methods

2.1. Inclusion criteria

We undertook a retrospective multicenter analysis in 798 children (aged 0–18 years) managed by EC in 5 clinics between 2012 and 2017 (1159 renal units [RU]). In all patients, EC was performed by the same surgeon in each of the 5 institutions. In all patients, PPC was used as the bulking agent. The patients were diagnosed based on voiding cysto-urethrography (VCUG) results. The reflux grade was determined according to the classification of the International Reflux Study Committee (IRSC). EC was carried out in case of high reflux grades (IV-V), signs of renal scarring based on dimercaptosuccinic acid (DMSA) scan or functional magnetic resonance urography, or recurrent febrile urinary tract infection (UTI) while on antibiotic prophylaxis.

We prescribed antibiotic prophylaxis in all children with VUR grades III-V up to the age of 1 year, as well as in children with VUR of any degree with a history of symptomatic UTI. We also prescribed antibiotic prophylaxis in children aged >1 year suffering from VUR and urinary tract dysfunction.

2.2. Exclusion criteria

We excluded patients with incomplete data sets and patients in whom bulking agents other than PPC were injected for EC of VUR. Incomplete data sets were for those of patients who refused further monitoring (for various reasons). Patients with upper urinary tract duplication or neurogenic bladder dysfunction were also excluded from this investigation.

2.3. EC injection technique

All patients received antibiotic prophylaxis prior to EC.

Endoscopic treatment was performed using a Karl Storz Pediatric Cysto-Urethroscope (9.5 French) with a direct working channel (Karl Storz, Tuttinglen, Germany). We used a semi-rigid metal needle (Vantris needle 3.6 French, length 350 mm) to insert the implant. As an implant, we used PPC, namely Vantris (HTG – Healthcare Technologies, Berlin, Germany).

The median and quartile range [Q1; Q3] of volume of injected bulking agent was 0.4 [0.3; 0.5] mL.

The PPC injection technique was adjusted to the anatomic features of the ureteral orifice. When using the STING technique, the needle was inserted at 6 o’clock position at a distance of 3 mm from the orifice of the refluxing ureter to a depth of 5 to 6 mm. The orifice was raised on the needle and the implant was inserted until a bump was formed.

When using the HIT technique at the background of hydrodistension of ureteric orifice, a needle was inserted at a 6 o’clock position into the submucosa of the intramural ureter, at a distance of about 4 mm from the entrance to the orifice. The implant was injected until the orifice had closed.

The HIT method was used for a wide orifice (type H2 and H3 according to the classification proposed by Cerwinka et al in 2008[8]), while STING was used in all other cases.

A follow-up VCUG was performed 4 to 6 months after EC.

2.4. Follow-up of patients

Clinical and renal ultrasound examinations were carried out before EC, 1 day and 1 month after EC, and then every 6 months after EC up to 5 years thereafter. Patients exhibiting pelviccaliceal dilatation underwent hydronephrosis grading in accordance with the SFU classification.[13] In case of suspected UVJO, voiding cysto-urethrography was performed. In the absence of VUR, we obtained dynamic diuretic renal scintigraphy. UVJO was confirmed if ureteral and pelviccaliceal dilatation persisted, coupled with diuretic renal ultrasound findings indicating obstruction exceeding the values recorded prior to EC.

Repeated EC was performed in patients with persistent VUR grade which had not decreased or with VUR grade that had increased after the first EC, and in case of recurrence of UTI in combination with persistent VUR of any grade.

2.5. Treatment of UVJO

When the first patients (12 cases) with UVJO were identified, we used ureteral JJ-stents to eliminate the obstruction. However, we identified persistent ureteral and pelviccaliceal dilatation in these patients according to ultrasound data within 1 month after removal of the JJ-stent. Ureteral and pelviccaliceal dilatation after removal of JJ-stents did not differ from the values measured by ultrasound before the JJ-stent placement. Thus, we abandoned the use of JJ-stents in UVJO patients treated thereafter.

UVJOs were corrected using transurethral evacuation of the implant and Cohen ureteral re-implantation. During cystoscopy, the bladder mucosa overlying the PPC bulge was dissected. Subsequently, the PPC implant was fragmented and evacuated into the bladder cavity. Fragments of the bulking agent were removed from the bladder transurethrally.

2.6. Statistical analysis

For descriptive statistics, we used median and quartile ranges (lower and upper) for continuous variables and number/percentage for categorical data. For comparison of risk factors for late obstruction, we used the Mann–Whitney nonparametric test for continuous variables and the χ2 test (Yates’s) for categorical variables. Logistic regression was used for multivariate analysis. The significance of regression coefficients was analyzed, and odds ratios (OR) and 95% CIs were estimated.

Receiver operating characteristic (ROC) analysis was performed to compare the forecast quality and select the best models.
For each model, a ROC curve was built and a threshold level corresponding to the best combination of sensitivity and specificity was selected. Next, the models were compared by area under the curve (AUC), as well as sensitivity and specificity for the selected threshold level.

Additionally, we analyzed the classification error matrix to determine the number of false-positive, false-negative, true-positive, and true-negative results.

The critical value of the level of statistical significance when testing null hypotheses was assumed to be 0.05. Statistical analysis and processing of the collected data were performed in R (version 3.2, R Foundation for Statistical Computing, Vienna, Austria).

2.7. Approval by Ethics Committee

This study was approved at the Local Independent Ethics Committee of the Federal State Budgetary Institution of Higher Education “Rostov State Medical University”, Russian Federation. The Local Independent Ethics Committee panel session was held on January 25, 2018 (number of protocol: 2/18).

3. Results

The study population of 798 patients comprised 464 girls (58.1%) and 334 boys (41.9%). Right-sided VUR was present in 190 (26.0%), left-sided VUR in 247 (33.8%), and bilateral VUR in 361 (49.5%) children. Median age of patients was 39 months (range: 1–214 months; Q1:17; Q3:78). Grade I VUR was present in 34 (2.9%) RU, grade II VUR in 299 (25.8%) RU, grade III VUR in 594 (50.2%) RU, grade IV VUR in 206 (17.8%) RU, and grade V VUR in 26 (2.2%) RU. Median reflux grade was 3 [Q1: 2; Q3: 3]. STING procedure was used in 708 (88.7%) patients comprising 1035 RU (89.3%) treated. The HIT method was applied in 90 (11.3%) children involving 124 RU (10.7%).

After the first injection, VUR was eliminated in 692 (86.7%) patients and after the second injection, reflux was eliminated in 37 (4.6%) children. Overall success rate was 91.4% after 1 or 2 PPC injections for EC of VUR (729/798 children).

Table 1 shows renal ultrasound findings categorized according to SUF classification obtained postoperatively from day 1 to 6 months.13

Two groups of patients were formed, i.e., group I consisting of patients who had no UVJO, and group II comprising the children with confirmed UVJO. Group I comprised 754 children (449 [59.5%] girls and 305 [40.5%] boys) with 1114 RU affected. Median age of the children in group I was 41 months (range: 1–214 months; Q1: 18 months, Q3: 81 months). The STING technique was used in 690 (91.5%) children with 1017 RU (91.3%) affected, while the HIT method was applied in 64 children (8.5%) with 97 RU affected (8.7%).

Group II comprised 44 (5.5%) children (29 [65.9%] boys) and 15 [34.1%] girls with 45 RU (3.9%) affected. Their median age was 21.5 months (range: 3–122 months; Q1: 12; Q3: 43). UVJO developed in 33 (75.0%) children after the first injection and in 11 (25.0%) children after the second injection. The STING procedure was used in 18 (40.9%) cases with 18 RU (40%), while the HIT method was applied in 26 (59.1%) children with 27 RU (60%) treated. One child suffered bilateral obstruction after injection of PPC using the HIT method.

All patients with obstruction had hydrourephrosis (SUF grade III–IV). Overall, 11 (25%) children complained of abdominal pain. Among the patients in the second group, UTI was registered in 12 (27.2%) children. During the first 6 months after EC, symptomatic UTI occurred in 5 (41.6%) patients. Asymptomatic bacteriuria occurred in 7 (59.4%) patients within the period from 3 to 36 months after EC.

In order to eliminate the obstruction, our first-line surgical intervention was cystoscopic widening of the ureteral orifice extension followed by insertion of a JJ-stent in 12 (27.3%) patients. In 4 (9.1%) patients, we performed a dissection of the mucosal layer overlying the PPC bump with subsequent fragmentation and evacuation of the bulking substance.

After removing the JJ-stent, an open (10 [22.7%] patients) or vesicoscopic (2 [4.5%] patients) Cohen ureteral re-implantation was performed because JJ-stenting proved unsuccessful.

Overall, 17 (38.6%) children underwent open and 11 (25%) children underwent vesicoscopic Cohen ureteral re-implantation.

Ureteral re-implantation after EC using PPC proved technically considerably more difficult (at the stage of mobilization of the distal ureter) in comparison to re-interventions after EC using hyaluronic acid dextranomer or polycrylamide gel, especially in cases where the intervention was performed during the first year after endoscopic treatment.

Comparison of the patients’ median ages in groups I and II revealed that the median age was lower in the group of patients who developed UVJO (group II). Thus, the risk of developing OC was higher in younger children (P < .001).

Median VUR grade in group I was 3 (Q1:2; Q3:3). Median VUR grade among children with UVJO (group II) amounted to 4 (Q1:3; Q3:4). A comparative study to estimate UVJO frequency among the patients of either groups revealed that the UVJO risk was higher in patients with high reflux grades (P < .001).

Analysis of gender composition in groups I and II demonstrated that the probability of UVJO development was significantly higher for boys than girls (P < .001). Moreover, the risk of UVJO development when using the HIT method was higher when compared to the STING technique (P < .001; Table 2).

| Table 2 Gender distribution and technique of endoscopic correction (n = 798). | Group 1 | Group 2 |
|---|---|---|
| **Gender** | **Abs.** | **%** | **Abs.** | **%** |
| Boys | 305 | 40.5 | 29 | 65.9 | P < .001 |
| Girls | 449 | 59.5 | 15 | 34.1 | |
| **Technique** | | | | |
| STING | 690 | 91.5 | 18 | 40.9 | P < .001 |
| HIT | 64 | 8.5 | 26 | 59.1 | |

HIT = hydrodistension implantation technique, STING = subureteral transurethral injection.
A second PPC injection was administered in 82 (10.3%) children to correct recurrence of VUR. UVJO after the first injection was detected in 33 (4.6%) patients. Among the children who had undergone a second EC, obstruction was diagnosed in 11 of 82 (13.4%) children. We found a statistically significant increase of UVJO risk following the second injection (P=0.003; Table 3).

In patients in group II, OC was detected within 5 years after EC. During the first year after EC, UVJO occurred in 29 (65.9%) children. During the next 2 years, UVJO developed in 11 (25.0%) children. In 3 (6.8%) patients, UVJO developed during the fourth year after EC. In 1 (2.3%) patient, UVJO occurred during the fifth year after EC (Fig. 1).

In 22 of 29 (75.9%) children with UVJO developing during the first year after EC, the HIT method was used. The second injection using the STING technique resulted in UVJO development after EC in 8 of 15 (53.3%) patients during a period of 2 to 5 years after EC.

Multivariate regression analysis showed that UVJO was associated with 4 risk factors, i.e., male gender (OR 2.57; 95% CI, 1.29–5.23; P = 0.0078), age (OR 0.98; 95% CI, 0.97–0.99; P = 0.0044), EC injection technique, HIT versus STING (OR 0.07; 95% CI, 0.03–0.13; P < 0.0001), and second injection of PPC (OR 2.63; 95% CI, 0.99–6.38; P = 0.04).

Affected kidney side (OR 0.58; 95% CI, 0.29–1.15; P = .12) and grade of VUR (OR 1.23; 95% CI, 0.82–1.87; P = 0.31) showed no statistically significant association with UVJO (Table 4).

A logistic regression model was built after the exclusion of non-significant risk factors (AUC=88.43%, Fig. 2). Table 5 shows coefficients of logistic regression, ORs (95% CI), and P-values.

Risk of UVJO can be calculated using the following formula:

\[
\text{Risk of UVJO} = \text{logistic}(-1.23 + 0.97 \times \text{Gender} - 0.02 \times \text{Age(month)}^3 - 2.79 \times \text{Technique = STING}^7 + 1.12 \times \text{of injection}^7)
\]

For this ROC curve, the optimal balance of sensitivity and specificity was achieved at a threshold level of 3.8%, which provided the highest diagnostic accuracy of 81%. Sensitivity of the model was 78%, and specificity was 81%.

4. Discussion

In all clinics involved in this study, PPC injections for correction of VUR had been used since 2012. The majority of surgeons who began to use PPC for EC had gained their experience with other implants. PPC can be applied successfully to increase the success rate of EC correction of VUR at a low rate of subsequent UVJO, as long as its properties are kept in mind. Decreasing the injected PPC volume has become the first step in reducing the risk of UVJO. In one of the first papers dedicated to the outcomes of PPC application, Chertin et al reported an average volume of injected PPC of 0.8 mL. In 2015, other authors reported an average volume of 0.6 mL of injected volume of PPC used in EC interventions. A multicenter survey published in 2014 reported favorable results after a reduction of the average bolus volume to 0.4 mL. We took this experience into account, and therefore, the average volume of PPC bulking agent used in our study was 0.4 [Q1:0.3; Q3:0.5] mL.

![Figure 1. Time point of uretero-vesical junction obstruction formation and mode of polyacrylate-polyalcohol copolymer injection.](Image)

Table 3

| Table 3 | Uretero-vesical junction obstruction after the first and second injections of polyacrylate-polyalcohol copolymer. |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | Number of UVJO                                                                                                      |
|         | Total | Abs. | %   | P          |
| 1st injection | 692   | 33   | 4.8 | 0.003      |
| 2nd injection | 82    | 11   | 13.4|            |

Table 4

| Table 4 | Multivariate logistic regression analysis of risk factors for late obstruction after endoscopic treatment. |
|---------|---------------------------------------------------------------------------------------------------------|
|         | Odds ratio [95% CI] | P          |
| Gender (male) | 2.57 [1.29; 5.23] | 0.0078     |
| Age (mo) | 0.98 [0.97; 0.99] | 0.0044     |
| Side (left) | 0.58 [0.29; 1.15] | .12        |
| Grade of VUR | 1.23 [0.82; 1.87] | .31        |
| Technique (HIT vs STING) | 0.07 [0.03; 0.13] | <.0001     |
| Number of injection (second vs first) | 2.63 [0.99; 6.38] | .04        |

HIT = hydrodistension implantation technique, STING = subureteral transurethral injection.
In 2019, Alizadeh et al reported that decreasing the volume of injected PPC minimizes the risk of UVJO thus preserving the effectiveness of EC correction of VUR.[18] Therefore, we were not fully aware of the risks associated with injecting large volumes of PPC bulking agent at the time of treatment of the earliest patients in our study.

In a comparison of dextranomer/hyaluronic acid and PPC as bulking agents to treat VUR, Alizadeh et al demonstrated significantly better outcomes for PPC regarding the resolution of VUR (92.2% vs 75.7%).[18] The frequent development of UVJO after PPC injections during EC (3%–4%) remains a significant factor counterbalancing the effectiveness of EC, thus limiting the use of PPC.[11,12]

Garcia-Aparicio et al warned that the distal ureter had to be excised in all patients during ureteral re-implantation due to UVJO after PPC injection, because of massive periureteral fibrosis caused by injection of PPC bulking agent.[19] Our surgical experience showed that the described fibrosis complicates open and vesicoscopic ureteral re-implantation, especially if the reintervention was performed within the first year after PPC injection. Ureteral re-implantations performed more than a year after EC using PPC proved technically simpler but still more difficult than operations performed after injection of dextranomer/hyaluronic acid.

Prolonged postoperative observation is necessary after PPC-based EC of VUR. The longer the observation period, the higher is the frequency of UVJO. Warchol et al published the results of their 5-year monitoring of patients after EC.[20] UVJO occurred in 8% of patients within an interval of 1.1 to 2.9 years; the authors reported that ultrasound scanning was performed every 6 months after the operation. According to the multicenter survey data, UVJO incidence during a 3-year follow-up period after the operation was 1.2%. According to our evidence, UVJO can occur as late as 5 years after EC involving the use of PPC.

Ben-Meir et al hypothesized that a high grade of VUR affects the frequency of UVJO development.[21] The authors reported UVJO development in 9 of 480 (1.9%) patients who had undergone EC of high VUR grades (grades III–V) with PPC and hyaluronic acid copolymer.[21] These frequencies are lower than the rate of 5.5% of UVJO in our patients treated with PPC injections for EC correction of VUR. The median time interval between operation and diagnosis of OC in their group of patients was 12 months (range: 6–36 months).[21] In contrast (see Fig. 3), we noted a peak of OC occurrence at 4 to 12 months after EC of VUR using PPC, and a time range of 1 to 60 months until occurrence of UVJO. In a recently published article, Friedmacher

| Table 5 |
|---|---|
| Parameters of logistic regression model of risk factors for late obstruction after endoscopic treatment. | | |
| | Coefficient of logistic regression | Odds ratio [95% CI] | P |
| Gender (male) | 0.97 | 2.63 [1.35; 5.28] | .005 |
| Age (mo) | −0.02 | 0.98 [0.97; 0.99] | .003 |
| Technique (HIT vs STING) | −2.79 | 0.06 [0.03; 0.12] < .0001 |
| Number of injection (first vs second) | 1.12 | 3.07 [1.2; 7.21] | .013 |

HIT = hydrodistension implantation technique, STING = subureteral transurethral injection.
and Puri reported that the occurrence of UVJO varied from immediately after the procedure to 63 months, which is in agreement with our results.122

Duration of the obstruction determines the magnitude of damage to the kidney tissue. The longer the obstruction persists, the higher the probability of progression of renal tissue damage even after relief of the ureteral obstruction.123,24 In this context, our results demonstrate the need for regular and long-term monitoring of patients after EC with the use of PPC.

Only 1 publication related the effect of implant injection technique to the incidence of obstructions. Karakus et al reported on 7 (14%) patients who suffered UVJO after EC. Six of their patients had undergone double HIT procedure.25 The results of our study confirmed their findings that the HIT technique employing PPC injections as a bulking agent should be applied with caution. Karakus et al concluded that the increased risk of UVJO development in infants is partly caused by the small dimensions of the ureter and functional immaturity of the lower UVJO development in infants is partly caused by the small dimensions of the ureter and functional immaturity of the lower

UVJO development in infants is partly caused by the small dimensions of the ureter and functional immaturity of the lower urinary tract.25 From their analysis of factors affecting the risk of UVJO after EC, Chertin et al concluded that a high grade of VUR, presence of a refluxing megaureter with UVJO signs, and inflamed bladder mucosa were the only reliable risk factors for the development of UVJO.26 The authors did not rule out a role of PPC injection mode and pointed out the need for further research in this area.26 The observation of an increased risk of UVJO with younger age due to a smaller ureter appears somewhat contradictory to the increased risk of UVJO with wider ureter due to high-grade VUR. We speculate that due to the fast growth of the ureter-vesical junction complex in very young children, scarring caused by PPC injection to correct high-grade VUR may constitute a relatively greater risk of UVJO despite the smaller PPC volume used in young children. This hypothesis may explain the observation of a higher rate of UVJO in younger children treated with PPC injection for high-grade VUR compared to older children, even if the ureteral orifice appeared wide at the time of endoscopic intervention.

4.1. Study limitations and strengths

Due to incomplete data sets and loss of follow-up, a number of patients had to be excluded from our long-term follow-up investigation. Owing to the retrospective design of this investigation, our results must be interpreted with caution.

The strength of our multicenter study was the high number of patients and the long-term follow-up of patients.

5. Conclusions

Our study showed that in addition to the known risk factors of UVJO development after EC (such as large volume of PPC), young age, male gender, HIT technique, and a second PPC injection to correct recurrent UVJO were factors associated with the risk of UVJO. Patients who underwent EC using PPC must be followed up for at least 5 years to detect late occurrence of UVJO. We hypothesize that the favorable outcomes of PPC-based EC can be preserved if the identified risk factors are borne in mind.

Author contributions

Vladimir V. Sizonov, MD, PhD - development of research design, surgical interventions, obtaining data and material for research, analysis of the data obtained, review of publications on the topic of the article, manuscript writing.

Ilya M. Kagantsov, MD, PhD – obtaining data and material for research, surgical interventions.

Johannes M. Mayr, MD, PhD – amending the text of the manuscript, final approval of the article.

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Aleksandr V. Pirogov, MD – obtaining data and material for research, surgical interventions.

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