

Usefulness of intraoperative voiding cystourethrogram as an indicator of success in the endoscopic treatment of vesicoureteral reflux

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ABSTRACT

Objective. Up until now, serial voiding cystourethrogram (SVCU) has been regarded as the gold standard technique in the diagnosis of vesicoureteral reflux (VUR). The aim of intraoperative SVCU during endoscopic treatment is to detect those patients eligible to receive more biosynthetic material as a result of persistent VUR. The objective of this study was to assess the usefulness of SVCU as a predictor of treatment success.

Materials and methods. An analytical, retrospective study of patient medical records was carried out. Patients included had undergone endoscopic VUR surgery from 2000 to 2019, and they were measured in ureteral units. VUR persistence at intraoperative SVCU following treatment was compared with SVCU results after 3 months.

Results. Of a total of 167 ureteral units undergoing surgery, persistent reflux immediately after surgery was observed in 17 cases (10% of the sample). Only 3 cases had other urological malformations. In the SVCU carried out after 3 months, reflux was found in 38% of the sample (64 cases). When comparing the results, intraoperative SVCU demonstrated a specificity of 92.6%, and a sensitivity of 15.6%.

Conclusions. Given the low sensitivity (15.6%) of intraoperative SVCU to detect cases of persistent reflux in the mid-term, and considering the risks associated with radiation in the pediatric population – which is extremely sensitive to it –, intraoperative SVCU should be ruled out as a useful indicator of endoscopic treatment success.

KEY WORDS: Vesicoureteral reflux; Intraoperative cystourethrogram; Endoscopic treatment; Dextranomer/hyaluronic acid copolymer; Polydimethylsiloxane.

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UTILIDAD DE LA CISTOURETROGRAFÍA MICCIONAL INTRAOPERATORIA COMO INDICADOR DE ÉXITO DEL TRATAMIENTO ENDOSCÓPICO DEL REFLUJO VESICoureTERAL

RESUMEN

Objetivo. La cistouretrografía miccional seriada (CUMS) ha sido hasta ahora el gold standard en el diagnóstico del reflujo vesicoureteral (RVU). La finalidad de la CUMS intraoperatoria durante el tratamiento endoscópico es detectar aquellos pacientes subsidiarios de inyectar más material biosintético por persistencia del RVU. En este estudio hemos querido evaluar la utilidad de esta prueba como predictor de éxito del tratamiento.

Material y métodos. Estudio analítico retrospectivo mediante la revisión de historias clínicas de pacientes, medidos en unidades ureterales, intervenidos de RVU de forma endoscópica entre los años 2000 y 2019. Se comparó la persistencia de RVU en la CUMS intraoperatoria tras el tratamiento con el resultado de la CUMS a los 3 meses.

Resultados. De un total de 167 unidades ureterales intervenidas, se observó persistencia del reflujo inmediatamente tras la intervención en 17 casos (10% de la muestra). Solo 3 asociaban otras malformaciones urológicas. En la CUMS a los 3 meses se observó reflujo en el 38% de la muestra (64 casos). Al comparar los resultados, obtenemos para la CUMS intraoperatoria una especificidad del 92,6% y una sensibilidad del 15,6%.

Conclusiones. Dada la baja sensibilidad (15,6%) de la CUMS intraoperatoria para detectar los casos en los que persiste el reflujo a medio plazo y, teniendo en cuenta los riesgos asociados a la radiación que supone en una población especialmente sensible como es la pediátrica, se desestima su utilidad como indicador de éxito del tratamiento endoscópico.

PALABRAS CLAVE: Reflujo vesicoureteral; Cistouretrografía intraoperatoria; Tratamiento endoscópico; Copolímero de ácido hialurónico dextranómero; Polidimetilsiloxano.

INTRODUCTION

Up until now, serial voiding cystourethrogram (SVCU) has been the gold standard technique in the diagnosis of vesi-

coureteral reflux (VUR). There are two types of VUR – passive VUR, during bladder filling, and active VUR, during spontaneous voiding⁽¹⁾. The main drawback of SVCU is the fact it is an invasive, ionizing test. Therefore, an increasing number of studies support the role of ultrasound cystography in the diagnosis and follow-up of VUR⁽²⁾.

VUR treatment may be endoscopic or involve ureteral re-implantation surgery, with Cohen's intravesical technique being the most common one⁽³⁾. In the last years, endoscopic treatment has emerged as a less invasive alternative, with good results. Consequently, it has become the first therapeutic option in many cases. There are various techniques available. The most common one is the Sting (subureteric transurethral injection) technique⁽⁴⁾. HIT (hydrodistension implantation technique), which requires an intraureteral injection, is another possibility, with similar efficacy rates⁽⁵⁾. Today, the most widely used substance is dextranomer/hyaluronic acid (Dx/HA) copolymer, but there are other options available, such as polydimethylsiloxane and polyacrylate-polyalcohol copolymer⁽⁶⁾. The main drawback of these materials is the fact they tend to be partially reabsorbed. Therefore, treatment repetition is not infrequent during follow-up, especially in high-grade VUR. Intraoperative SVCU is carried out to ensure sufficient material has been injected for VUR healing purposes. Its usefulness will be assessed in this study.

MATERIALS AND METHODS

In our institution, all pediatric patients requiring surgical treatment of VUR are initially treated with an injection of Dx/HA or polydimethylsiloxane according to the Sting technique – Dx/HA has been predominant in the last years. Treatment criteria include repeated urinary tract infections (UTIs), increased urinary tract dilatation at ultrasonography, and/or impaired differential renal function (<40% or >5% reduction). Patients under of 1 year of age were treated as a result of repeated pyelonephritis, in spite of the various prophylactic antibiotic regimens used. This procedure is repeated up to 3 times according to the department's protocol. In these cases, the substance used is the same as in the initial treatment.

To confirm VUR repair, intravesical contrast is introduced, and the bladder is filled up to the expected bladder capacity (EBC) for each age – EBC is calculated according to the “30 + (age x 30)” formula. The objective of this is to induce urination and spontaneous voiding when the patient – who is placed on a superficial anesthetic plane – wakes up, which will also reveal active VUR – if present. The patient should be placed on a plane allowing for spontaneous voiding while asleep and under analgesia, which requires administration of inhaled sevoflurane, while avoiding muscle relaxants and intravenous opioids. In case of persistent VUR at radiological control, a new injection is

carried out. Once additional material has been administered, no further radiological controls are required if the limit of injected amount has been reached – as per the physician's visual control. A new imaging control would imply further radiation without changing therapeutic attitude.

In this context, decision was made to analyze SVCU's usefulness as a predictive factor of treatment success. An analytical, retrospective study of medical records of patients diagnosed with primary VUR and endoscopically treated from January 1, 2000 to May 31, 2019 was carried out. Data was analyzed as ureteral units (UUs). Epidemiological variables (age, sex) and VUR-related variables (laterality, presence of bilateral VUR, grade according to the International Reflux Study Committee classification, and association with other urological malformations such as ureteral duplicity, ectopic ureter, and ureterocele) were collected. VUR grades I-II were considered as low, whereas VUR grades III-V were considered as high. Treatment-related variables collected included date of surgery, type and amount of material injected, persistence of VUR at intraoperative SVCU, amount of extra material used in the presence of VUR, overall endoscopic treatments, and need for open surgery as a result of persistent VUR associated with clinical signs or worsening of renal function.

To assess the efficacy of intraoperative SVCU, SVCU results were compared with those from a new SVCU conducted 3 months following treatment. Successful treatment was defined as those cases where no VUR was observed at the SVCU carried out after 3 months. Cases where VUR diminished but did not completely disappear were not included in the successful treatment group, even if they were asymptomatic and did not require a new surgery. This study was approved by the Ethics Committee of our institution. For data analysis purposes, the SPSS 25 statistical software was used.

RESULTS

In the 19 years covered by the study, 103 patients were included, which means a total of 167 UUs treated through endoscopic anti-reflux techniques. Mean age at first treatment was 3 years (4.5 months – 10.6 years). Female cases were predominant (57%). 37% of the individuals in the sample had other urological abnormalities, which are featured in Figure 1. VUR was bilateral in 62 patients. No predisposition in terms of laterality was noted (51% left vs. 49% right). VUR grade was distributed as shown in Figure 2. 79.8% of all VUR cases were high-grade VUR (grades III-V). In 9 cases, isolated grade II VUR was treated as it was associated with UTIs. The remaining UUs with low-grade VUR were treated as they were associated with contralateral high-grade VUR.

In our sample, of the 167 UUs, 45 (27%) were eligible for a second endoscopic treatment, and 12 (7.2%) were

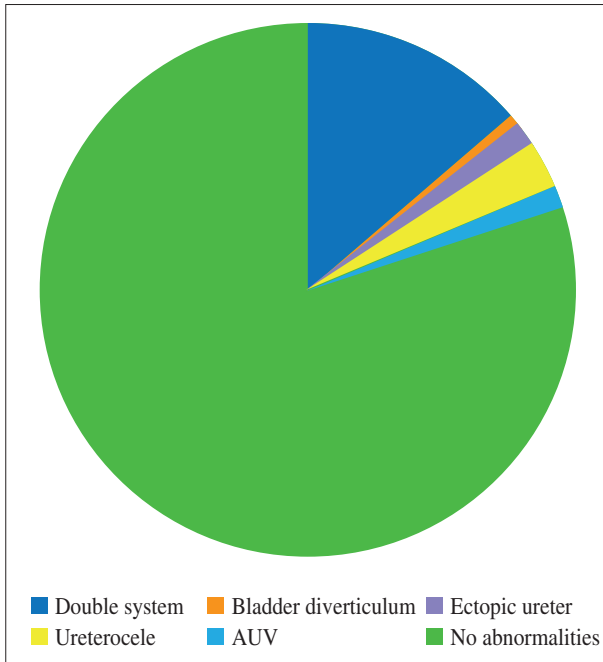


Figure 1. Association of VUR with other urological abnormalities. 37% of cases had further abnormalities – 23% were double systems, and 14% were other abnormalities.

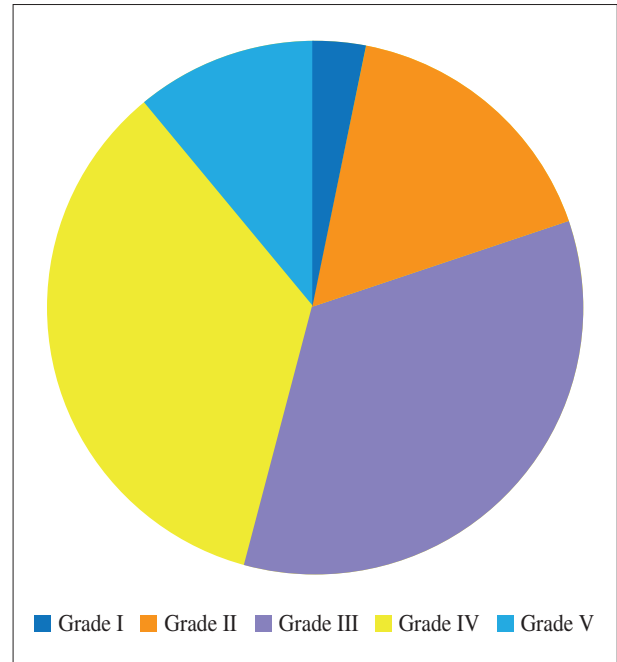


Figure 2. VUR grade distribution in the sample.

Table I. Success rates for each endoscopic treatment.

	VUR healing	Success rate
Surgery 1	100 out of 167 UUs	60%
Surgery 3	17 out of 45 UUs	37.8%
Surgery 3	8 out of 12 UUs	66.7%

eligible for a third one. Overall healing rate was 74.8% following 3 surgeries, but only 7.2% of cases required re-implantation surgery – in the remaining asymptomatic patients, low-grade VUR was observed. When analyzing each treatment, VUR healing rates were 60%, 37.8%, and 66.7%, respectively (Table I). In most low-grade VUR

cases, VUR was healed following one treatment (30 out of 33 UUs), whereas only 55% of high-grade VUR cases were healed in the first treatment. Table II features healing rates according to VUR grade. A statistically significant relationship was found between high-grade VUR and need for a greater number of endoscopic treatments ($p=0.024$).

Polydimethylsiloxane was used in 106 cases, and Dx/HA was used in 61 cases for the first treatment. Mean amount of biosynthetic material used was 0.78 cc (0.2-2 cc) in the first surgery, 0.78 cc (0.4-1.2 cc) in the second surgery, and 0.69 cc (0.4-0.8 cc) in the third surgery. VUR was healed in 38% of cases treated with polydimethylsiloxane, and in 42% of cases treated with Dx/HA. No differences in terms of success rates were found between the two materials used ($p=0.61$).

Intraoperative SVCU was performed in 159 UUs (95% of the sample), with persistence of VUR in 17 UUs

Table II. First treatment success according to VUR grade.

	Preoperative VUR	VUR at postoperative SVCU	Healing rate
Grade I	5	3	40%
Grade II	28	4	85.7%
Grade III	57	20	64.9%
Grade IV	59	33	44%
Grade V	18	7	61.1%
Total	167	67	60%

Table III. Intraoperative SVCU results vs. results from the SVCU carried out three months following treatment.

		SVCU D90		
		No	Yes	Total
Intraoperative SVCU	No RVU	88	84	142
	RVU	7	10	17
Total		95	64	159

(10.7%). Prevalence was higher on the left side, with 14% of all left ureters, vs. 6.1% of all right ureters ($p=0.08$). Regarding previous VUR grade, prevalence was higher in high-grade VUR – 8 grade III cases, 5 grade IV cases, and 2 grade V cases, with no statistically significant relationship ($p=0.39$). Of these 17 units, only 3 had further urological abnormalities associated – 1 ectopic ureter and 2 double systems with ureterocele. Consequently, no relationship was found between having another urological pathology and persistence of VUR at intraoperative SVCU ($p=0.13$). In all persistent VUR cases, a new injection of material was conducted to increase the size of the bleb in the vesicoureteric junction, without radiological control. Of these 17 cases, 4 had VUR at control SVCU following 3 months (23.53%).

At control SVCU following 3 months, VUR incidence had raised to 64 cases (38%) (Table III). Therefore, SVCU had a false negative rate (FNR) of 84.4%, and a true positive rate (TPR) of 15.6%. Based on this, specificity was 92.6%, and sensitivity was 15.6% (Table IV).

DISCUSSION

Endoscopic treatment as an initial therapy has gained increasing popularity in the last 20 years as it is less aggressive and offers good healing rates⁽⁷⁾. This is consistent with our results, with an overall success rate of 92.8%. Our results for the first (60%) and second (37%) surgery are similar to those published in the literature. In a 2018 study by Friedmacher et al. on 851 endoscopically treated patients, success rate was 69% following the first surgery, 20% following the second surgery, and 10% following the third surgery⁽⁸⁾. However, in our case, success rate following the third surgery was 66.7%, much higher than 10%. This could be explained by the fact open surgery was decided upon in some patients with persistent VUR following the second surgery, with the third endoscopic treatment being indicated in selected cases only.

Even though endoscopic treatment success is multifactorial, the literature widely acknowledges that VUR grade is the main factor to be considered, as reported in

Table IV. Analytical results of intraoperative SVCU.

True positive = 10	
True negative = 88	Specificity = 92.6%
False negative = 54	Sensitivity = 15.6%
False positive = 7	

the 2017 study by Kim et al.⁽⁹⁾. In our study, healing rates were higher in low-grade VUR than in high-grade VUR, with 90.9% of cases completely healed following the first surgery. This proportion is similar to that found by Kirsch et al. in their 292-UU series, with 90% for grade I VUR, and 82% for grade II VUR⁽¹⁰⁾. It is slightly higher than that described by Elder et al.'s meta-analysis of an 8,101-UU sample, with healing rates of 78.5% for low-grade VUR⁽¹¹⁾.

When it comes to assessing SVCU as a predictive factor of treatment success, there is certain controversy in the literature published. According to some studies, such as Palmer's⁽¹²⁾ and Wozniak et al.'s⁽¹³⁾, it is useful to identify cases eligible for repeated injection of material as a result of persistent residual reflux. In the case of Palmer, only 1 out of 64 UUs required re-injection⁽¹²⁾, whereas in Wozniak et al.'s, it was needed in 4 out of 17 UUs, which accounts for 24% of cases⁽¹³⁾. Both proportions are higher than that found in our study, which was just 10%. In addition, Palmer highlights it may be useful to treat newly emerged contralateral reflux, while pointing out there is not sufficient evidence to correlate results with those from a cystography performed after 3-4 months⁽¹²⁾. Similarly, in their study on 14 patients undergoing intraoperative SVCU with negative results, Perlmutter et al. found a FNR of 42.9%⁽¹⁴⁾. Therefore, according to them, intraoperative SVCU does not seem a good predictive factor of treatment success. This is similar to the conclusions drawn from our study, where sensitivity was just 15.6%, and FNR was 84.4%.

The factors that could explain the low performance of intraoperative SVCU include the nature of the substances used, which have a tendency towards partial reabsorption, and the fact SVCU does not match reality in patients under anesthesia. Today, Dx/HA is the most widely used substance – and the only approved by the Food and Drug Administration (FDA). However, although polydimethylsiloxane has not been approved in children yet, efficacy in the pediatric population has been widely acknowledged in the literature⁽¹⁵⁻¹⁷⁾. In our study, similarly to what Williams G et al. reported in their 2019 meta-analysis⁽¹⁸⁾, healing rates were similar with both materials. Their tendency towards partial reabsorption was described by Kirsch et al.'s study, where an 18% volume reduction was noted after 2 weeks, with an extra 1% 3 months following surgery⁽¹⁰⁾. Additionally, in a 2014 prospective study, López et al. assessed the correspondence between preoperative SVCU and intraoperative pre-treatment SVCU to deter-

mine whether intraoperative post-treatment SVCU would be useful to predict results. In this study, up to 60% of the 23 patients with VUR at preoperative tests 6 months before treatment had no VUR at the pre-treatment SVCU carried out under anesthesia. Consequently, the authors conclude that post-treatment SVCU is not useful to assess treatment results because of its low reliability under profound sedation⁽¹⁹⁾.

It should be noted that SVCU involves radiological exposure, and radiation effects are inversely proportional to patient age. Estimated risk of fatal cancer is 5%, as reported by Sievert⁽²⁰⁾. In a 2016 multi-center study, Suliman et al. measured the radiation generated by a voiding cystourethrogram conducted in 167 pediatric patients, with a mean of 0.03-0.4 mSv per procedure⁽²¹⁾. At <50 mSv doses, the association with cancer is not that clear. However, the “radiation is always detrimental” principle should be adopted, since any exposure to radiation may be harmful and should be avoided if unnecessary⁽²⁰⁾. In this respect, it should be mentioned that an increasing number of studies support the role of ultrasound cystography in the diagnosis and follow-up of VUR. This dynamic test has demonstrated effectiveness levels similar to SVCU’s in terms of VUR detection and gradation, with the additional advantage it does not imply radiation exposure^(2,22). It proves especially useful in the follow-up period, since it is highly sensitive for reflux detection. Its main drawback lies in the fact it does not allow the urethra to be accurately visualized, which is why some authors still believe SVCU remains a better option as a first diagnosis⁽⁴⁾. In addition, the highest image quality levels are achieved in patients under 2 years of age thanks to the echo-resonance of their tissues⁽²²⁾, and this is precisely the age range most of our patients fall within at diagnosis. In our institution, it is being increasingly used in the follow-up of VUR patients, and it will probably become the gold standard technique in the upcoming years.

In conclusion, the absence of VUR at intraoperative SVCU is not correlated with SVCU findings following 3 months, with a sensitivity of only 15.6% according to our study. This may be explained by the fact the biosynthetic materials used are prone to partial reabsorption, and also to the fact cystography is less accurate in terms of diagnosis in patients under anesthesia, even if conducted on a superficial plane allowing for spontaneous voiding. Therefore, considering the radiation involved, we believe it should not be used as a predictor of treatment success.

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