ORIGINAL ARTICLE

Prognostic factors of endoscopic treatment of vesicoureteral reflux in spinal cord injured patients

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Vesicoureteral reflux; Videourodynamic; Endoscopic treatment; Spinal cord injury

Abstract
Introduction: Vesicoureteral reflux (VUR) is an important complication in patients with spinal cord injury due to its frequency and morbidity. One of the most extended therapeutic options is endoscopic injection of obliteration substances in the urethral meatus.
Objective: To analyze the prognostic factors of VUR treatment using obliteration substances in patients with spinal cord injury.
Material and methods: A prospective study was performed in a cohort of 76 patients (age 48.9 ± 14.4 years), of both genders, with spinal cord injuries, who underwent endoscopic treatment of the VUR during the years 2008–2011. In all the patients, a clinical history was obtained and a pre-operative videourodynamic study was performed. Another study was carried out at 7.32 months (standard deviation: 6.28 months) of the intervention. Treatment consisted in endoscopic injection of dextranomer/hyaluronic acid copolymer (62 cases) and polydimethylsiloxane (14). The statistical tests applied were the Fisher’s exact test and the Student’s T test comparing the means. Bilateral significance level was established at 95%.
Results: Resolution of VUR was achieved in 46 cases (61%). The statistically significant prognostic factors were age (younger aging cured patients), bilaterality and reflects great (greater grade in bilaterality in the cases with persistence of reflux) and presence of neurogenic detrusor overactivity (greater percentage in the cases of reflux persistence). Stress urinary incontinence (greater percentage in cured patients), contractile potency (lower percentage in cured patients) and urethral resistance (greater percentage in cured patients) were also statistically significant prognostic factors.
Conclusions: Among the prognostic factors that affected the endoscopic treatment results of the VUR in patients with neurogenic lower urinary tract dysfunction (NLUTD), anatomical as well as functional factors were found.
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Factores pronosticos del tratamiento endoscopico del reflujo vesicoureteral en pacientes con lesion medular

Resumen

Introducción: El reflujo vesicoureteral (RVU) constituye una complicación importante en pacientes con lesión medular por su frecuencia y morbilidad. Una de las opciones terapéuticas más extendidas es la inyección endoscópica de sustancias obliteratoras en el meato ureteral. Objetivo: Analizar los factores pronósticos del tratamiento del RVU mediante sustancias obliteratoras en pacientes con lesión medular.

Material y métodos: Se realizó un estudio prospectivo en una cohorte de 76 pacientes (edad 48,9 ± 14,4 años), de ambos sexos, con lesión medular sometidos a tratamiento endoscópico del RVU, durante los años 2008 a 2011. A todos los pacientes se les realizó una historia clínica y un estudio videourodinámico preoperatorio y a los 7,32 meses (desviación típica: 6,28 meses) de la intervención. El tratamiento consistió en la inyección endoscópica de copolímero de ácido hialurónico (62 casos) y polimetrilisoxano (14). Las pruebas estadísticas aplicadas fueron el test exacto de Fisher y la prueba de comparación de medias de la t- Student. El nivel de significación se fijó en el 95% bilateral. Resultados: La resolución del RVU se consiguió en 46 casos (61%). Los factores pronósticos estadísticamente significativos fueron la edad (menor edad en los pacientes curados), la bilateralidad y el grado del reflujo (mayor grado y bilateralidad los casos de persistencia del reflujo) y la presencia de hiperactividad neurológica del detrusor (mayor porcentaje en el caso de persistencia del reflujo), la incontinencia urinaria de esfuerzo (mayor porcentaje en pacientes curados), la potencia contractil (menor en pacientes curados) y la resistencia uretral (mayor en pacientes curados).

Conclusiones: Entre los factores pronósticos que influyen en el resultado del tratamiento endoscópico del RVU en pacientes con disfunción neurológica del tracto urinario inferior (DNTUI) se encuentran tanto factores anatómicos como funcionales.

Introduction

Vesicoureteral reflux (VUR) is a complication of spinal cord injury. Its incidence varies; in patients with acute spinal cord injuries incidence is 12%. In these patients, VUR causes reflux nephropathy that, with other factors, results in renal failure. Moreover, a strong correlation between the presence of VUR and acute pyelonephritis and urinary sepsis is observed. Therefore its treatment is essential.

In the treatment of VUR it is necessary to distinguish between primary reflux and reflux secondary to a disorder in the lower urinary tract, in patients with neurogenic lower urinary tract dysfunction (NLUTD). Neuropenic detrusor overactivity (NDO) with perirethral sphincter dyssynergia (SD) is the major cause of secondary VUR and it is treated with anticholinergic agents. However, surgery is necessary when anatomic abnormality of ureteral meatus is observed.

Currently, the correction of incompetence of the ureteral meatus is performed by endoscopic implantation of substances that occlude it. Its employ is a habitual practice in the treatment of childhood VUR.

This treatment also has been used in patients with NLUTD with good results. However, this technique fails in a variable percentage. The objective of our study is to analyze the prognostic factors of endoscopic VUR treatment in spinal cord injury patients of both sexes. It is necessary to take into account that many of these patients show functional disturbances in the lower urinary tract (LUT), which may affect to the outcomes. For this reason, we considered important the video urodynamic study.

Material and methods

A prospective study was performed in a cohort of patients of both sexes, with spinal cord injury, diagnosed of VUR candidate for endoscopic treatment with obliteration substances. Inclusion criteria were VUR demonstrated on videourodynamics and the presence of stable spinal cord injury. Exclusion criteria were: no surgical indication in patients with reflux secondary to NDO treated with anticholinergic agents or patients refusal to undergo surgery procedure.

The size of the sample was calculated taking into account the study of Yucel et al. We considered a cure rate for VUR of 68%, and it was considered statistically significant when the difference with this rate was 27%. Assuming 5% alpha error and 80% statistical power, calculated sample size was 59 patients.

The patients included underwent a clinical history in which the level and grade of spinal cord injury and its time of evolution were detailed. Later, videourodynamic study with Solar system (MMS, Enschede, The Netherlands) was performed according to ICS specifications and GUP protocols.

Bladder was filled with radiological contrast at room temperature and at speed of 30 ml/s via 8-French two-way
transurethral catheter with patient lying in supine position. The intra-abdominal pressure was recorded using a transrectal balloon catheter. The filling phase ended when there was an involuntary detrusor contraction (NDO). During filling and voiding phase sequential video images were taken by radioscopic device (OEC Fluorostar; General Electric, USA) electronic connected to polygraph.

The following parameters were determined: functional bladder capacity (FBC), detrusor overactivity (DO), stress urinary incontinence (SUI), bladder-filling pressure (FP), maximum detrusor pressure (Pmax), urethral resistance measured by the URA parameter\(^{11}\) and detrusor pressure at maximum flow (Pw).\(^{12}\) VUR grade and location were also recorded. VUR grading was performed according to international system.\(^{13}\)

From June 2008 to November 2011, a total of 76 patients were intervened. Mean age was 48.9 ages (typical deviation: 14.4 years, interval between 13 and 75 ages). Sex distribution was 60 males (79%) and 16 females (21%).

Procedure consisted in uni- or bilateral submeatal endoscopic injection of obliteration substances until meatal closure with patient in 6:00hr. position. In 62 cases (82%) dextranomer/hyaluronic acid copolymer (Deflux\(^{®}\)) was used and polydimethylsiloxane (Macroplastique\(^{®}\)) in 14 (18%). In 9 cases (12%) a second injection was made. The absence of obstruction in the urinary tract after ureter meatal injection was confirmed in all cases.

At 7.32 months after surgery, patients were underwent to a second videourodynamic study (typical deviation: 6.28 months). In this phase, the cure or persistence of reflux was determined. The absence the reflux in renal units was considered as VUR cure, while it was the contrary for reflux persistence.

Data were recorded in ACCES\(^{®}\) database and exported to statistical software SPSS\(^{®}\) for its analysis. Statistical analysis was developed by Fisher exact test for dichotomous variables and T-Student’s test for parametric variables. Significance level was established bilateral in 95%.

### Results

#### Descriptive statistic

Distribution by grade and level of spinal cord injury is shown in Table 1. Time of evolution for spinal cord injury was 179 months (typical deviation: 138.5 months).

Distribution of urodynamic parameters is shown in Table 2.

#### Inferential statistic

Mean age of healing patients of VUR was 45.8 years (typical deviation: 13.9 years), mean age of non-healing patients of VUR was 53.0 years (typical deviation: 13.9 years). Differences were statistically significant (\(p = 0.033\)). Healing rate among male was 58% (35 cases), and among female 69% (11 cases). Differences were not significant.

Mean age of patients with unilateral reflux was 45.2 years (typical deviation: 14.9 years); mean age of patients with bilateral reflux was 53.2 years (typical deviation: 12.8 years). Differences were significant (\(p = 0.015\)).

63% of patients treated with hyaluronic acid were cured (39 patients); 50% of cases treated with polydimethylsiloxane were cured (7 patients). Differences were not significant. Of the re-operated patients 44% were cured (4 patients); patients operated for the first time were cured in 63% of cases (42 patients). Differences were not significant.

In healing patients, duration of the spinal cord injury was 174.08 months (typical deviation: 144.11 months), duration of injury was 192.97 months (typical deviation: 129.86 months) in non-healing patients. Differences were significant (\(p = 0.568\)).

73% of patients (30) with unilateral reflux were cured. 46% of patients (16) with bilateral reflux were cured. Differences were significant (\(p = 0.019\)). Relative risk (RR) of reflux

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### Table 1  Distribution of the level and degree of spinal cord injury of the patients in the study.

<table>
<thead>
<tr>
<th>C3-C8</th>
<th>D1-D6</th>
<th>D7-L2</th>
<th>L3-cauda equina</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>11</td>
<td>11</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Incomplete</td>
<td>10</td>
<td>7</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>18</td>
<td>31</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 2  Distribution of urodynamic parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional bladder capacity (mL)(^{a})</td>
<td>170 (118)</td>
</tr>
<tr>
<td>Detrusor overactivity(^{b})</td>
<td>53 (70%)</td>
</tr>
<tr>
<td>Stress urinary incontinence(^{b})</td>
<td>18 (24%)</td>
</tr>
<tr>
<td>Filling pressure (cm H(_2)O)(^{a})</td>
<td>8.30 (5.82)</td>
</tr>
<tr>
<td>Maximum detrusor voiding pressure (cm H(_2)O)(^{a})</td>
<td>37 (35.5)</td>
</tr>
<tr>
<td>URA (cm H(_2)O)(^{a})</td>
<td>24.15 (17.19)</td>
</tr>
<tr>
<td>Power at maximum flow (mW)(^{a})</td>
<td>7.49 (15.61)</td>
</tr>
</tbody>
</table>

\(^{a}\) Mean (standard deviation in brackets).

\(^{b}\) Absolute frequency (in brackets percentage).

### Table 3  Grade distribution and location of vesicoureteral reflux.

<table>
<thead>
<tr>
<th>Side reflux</th>
<th>Left</th>
<th>Right</th>
<th>Bilateral</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>7</td>
<td>11</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Grade II</td>
<td>4</td>
<td>9</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Grade III</td>
<td>6</td>
<td>3</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Grade IV</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>24</td>
<td>35</td>
<td>76</td>
</tr>
</tbody>
</table>

Location and degree of reflux (maximum degree of reflux given if bilateral) is shown in Table 3.

Reflux resolution was achieved in 46 cases (61%).
Persistence was 2.02 times higher among bilateral patients than among unilateral patients.

Percentage of patients with grade 1 reflux who were cured was 82% (18 patients), and percentage of patients with higher-grade reflux who were cured was 52% (28 patients). Differences were significant (p < 0.020). RR of reflux persistence among patients with higher-grade reflux was 2.64 times higher than among patients with grade 1 reflux.

Comparisons of urodynamic parameters are shown in Table 4. RR of reflux persistence among patients with OD was 2.82 times higher than among patients without OD. RR of reflux persistence among patients with SUI was 2.79 times higher than among patients without SUI.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Relationship between different urodynamic parameters and outcome of endoscopic treatment of reflux.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional bladder capacity (ml)</td>
<td>Endoscopic treatment outcomes</td>
</tr>
<tr>
<td></td>
<td>Healing</td>
</tr>
<tr>
<td>Detrusor overactivitya</td>
<td>180 (115)</td>
</tr>
<tr>
<td>Stress urinary incontinenceb</td>
<td>Yes: 27 (51%)</td>
</tr>
<tr>
<td>Filling pressure (cm H2O)c</td>
<td>8.85 (6.61)</td>
</tr>
<tr>
<td>Maximum detrusor voiding pressure (cm H2O)c</td>
<td>34 (42)</td>
</tr>
<tr>
<td>URA (cm H2O)c</td>
<td>31.30 (18.00)</td>
</tr>
<tr>
<td>Power in maximal flow (mW)c</td>
<td>34.09 (41.39)</td>
</tr>
</tbody>
</table>

\[ \text{a Mean (typical deviation in brackets).} \]  
\[ \text{b Absolute frequency (percentage in brackets).} \]  
\[ \text{c Significant.} \]

Discussion
In our study, 61% of VUR cases were resolved with endoscopic injections of obliterate substances; in other series, the success rate varies between 53%14 and 93%.15

The more contrasted prognostic factor is the reflux grade, both in childhood16 and in adults.17,18 In our study, RR of reflux persistence was 2.64 times higher in high-grade VUR. Bilaterality of VUR is related with reflux grade. VUR grade was higher in bilateral refluxes than in unilateral ones. It explains the worse prognosis of bilateral VUR.

Age has also proved to be other prognostic factor. Mean age of healing-patients was significantly lower than in no-healing patients. Ponce et al.19 have found that younger patients showed higher curing percentage. Our study has demonstrated that age is related with bilaterality of reflux (less frequent in younger patients). However, the duration of the injury did not affect treatment outcome. Therefore, it may be supposed that the influence of age has more to do with the own aging process than with effects over the time of spinal cord injury.

The type of substance used (hyaluronic acid or polydimethylsiloxane) was shown to have no significant influence on treatment outcomes. However, Moore et al.15 described higher successful rates with polydimethylsiloxane than with hyaluronic acid. Nevertheless, the lack of a randomized clinical trial precludes valid conclusions.

In our study, patients intervened for second time showed lesser curing percentage (44%) than those operated for first time (63%), although differences were not significant. Other authors, as Arce et al.20 have also referred less curing percentage in patients operated for second time (50% versus 69%), although there were no significant differences due to the small size of study population (26 patients).

The study of functional disorders of the LUT associated to reflux is critical to distinguish between primary and secondary reflux, and therefore, for the therapeutic indication. This diagnosis is only achieved by videourodynamic study, whereas that voiding cystography only allow the detection of reflux.20

In our study, only VUR non-associated with OD was treated; VUR associated with OD was treated with anticholinergic agents. Those VUR associated with OD cases in which reflux took place before involuntary contraction, were also underwent to endoscopic treatment. Salinas et al.21 have defined this type of reflux as evolved passive reflux because, although in a first phase the reflux was secondary VUR to OD, later it has conducted to an anatomical lesion in the meatus, evolving as primary VUR.

In normal conditions, pressure in vesicoureteral junction (UVJ) is greater than bladder pressure, both during filling and voiding phase.22 VUR takes place when bladder pressure is greater than pressure in UVJ. The change in the pressure gradient may appear in NLUTD caused by ureteral innervation injury as well as by functional obstruction in LUT in cases of OD associated with SD. The importance of OD per se in the origin and maintenance of reflux has not been investigated.22 In our study, OD patients had worse prognosis than patients with areflexia (reflux persistence probability was 2.82 times), although in all cases reflux occurred before involuntary contraction (evolved passive reflux).9 Arce et al.17 also got worse results in patients with neurogenic or idiopathic detrusor overactivity. Haferkamp et al.22 obtained worse long-term postoperative results (8 years) in a group of patients with myelomeningocele and bladder areflexia.
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However, these patients showed detrusor filling pressure (28 cm H$_2$O) considerably higher than patients of our series (8.30 cm H$_2$O).

By the other side, treatment outcome was independent of bladder capacity, i.e., when reflux took place after overactivity, treatment outcome was independent of the bladder capacity in the moment in which reflux appeared. Detrusor power measured in power at peak flow did show to have prognostic importance. Detrusor power was higher in patients in whom reflux persisted. Patients with higher contractile power develop higher pressure along contraction, favoring the reflux.

On the contrary, SUI has proved to be a good prognostic factor regarding healing of reflux. In our study, patients without SUI had RR of reflux persistence 2.79 times higher than those with SUI. This protective action may be explained because SUI reduces the gradient of urethral pressure, maintaining the pressure in the UVJ flowing urine through the urethra, avoiding in this way the reflux.

Finally, it is noteworthy that the urethral resistance value measured by the URA parameter was lower in patients with reflux persistence. Greater urethral resistance usually increases the pressure during voiding favoring reflux. However, in our series, this cause-effect relationship does not occur, because the reflux appeared during bladder filling.

Shafik has described a reflex relationship between the behavior UVJ and urethral sphincter mechanism to share the innervation. Thus, a disturbance in urethral resistance was translated into injury at the ureteral valve mechanism. Furthermore, one of the factors influencing the failure of endoscopic surgery of reflux is the level of meatus incompetence.

Conclusions

Prognostic factors that affect the endoscopic treatment outcomes of the VUR in patients with NLUTD are anatomical factors (reflux grade and bilaterality) as well as functional factors (OD and SUI).

Conflict of interest

The authors declare that they have no conflict of interest

References


