Original paper

Urodynamic evaluation before and after continuous intrathecal Baclofen infusion (ITB) in patients unresponsive wakefulness syndrome and minimally conscious state

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Abstract: Only a few reports have been published on acquired brain injury (ABI), especially on the correlation of urodynamic findings. The aim of this study is to urodinamically assess bladder function in patients on Unresponsive Wakefullness Syndrome (UWS) and Minimally Conscious State (MCS) before and after Intrathecal Baclofen Therapy (IBT) for supraspinal spasticity. After IBT there was a significant increase of Maximum Cystometric Capacity (MCC) and a reduction of Detrusor Leak Point Pressure (DLPP). Accordingly, an increase in Post Void Residual PVR in the first month was identified. While these results may seem a positive consequence of the therapy, they must be related to the type of patient treated, indeed the absence of a detrusor contraction supported by supraspinal centres can create an increase of the post-void residual. However, this discrepancy was filled out six months after implantation and the PVR returns comparable to the baseline.

Keywords: Intrathecal Baclofen therapy; Minimally conscious state; Unresponsive wakefullness syndrome; Urodynamics.

INTRODUCTION

Spasticity of either spinal or supraspinal origin may compromise patients severely and is associated with the development of pain, limb contractures and immobility.

Spasticity of supraspinal origin is much more common than spinal spasticity, but treatment with Intrathecal Baclofen Therapy (IBT) has been evaluated far less frequently in this condition[1].

Baclofen is a structural GABA analogue substance acting on the GABA-B receptor subtype. It is assumed to act at the spinal level attenuating mono and polysynaptic conduction, primarily by inhibiting the release of excitatory transmitters. Baclofen hardly penetrates the blood-brain barrier; therefore, penetration into the cerebrospinal fluid is poor with oral administration.

Only a few reports have been published on acquired brain injury (ABI), especially on the correlation of urodynamic findings. The most commonly expected urodynamic abnormality after ABI is involuntary detrusor contraction, which can be induced by the loss of cortical inhibition caused by suprapontine lesions. Very little is known about changes in urodynamic pattern in patients in Unresponsive Wakefullness Syndrome (UWS) and Minimally Conscious State (MCS). UWS and MCS are chronic disorders of consciousness that can follow ABI. UWS is defined by four criteria[2]: 1) no evidence of awareness of the self or the environment 2) no evidence of purposeful or voluntary response to external stimuli 3) no evidence of language expression or comprehension and 4) preserved EEG sleep-wake cycles. MCS occurs when reproducible, even if minimal, evidence of awareness is observed[3].

The aim of this study is to urodinamically assess bladder function in patients on UWS or MCS before and after IBT.

MATERIALS AND METHODS

We enrolled for this study 16 patients (13 males and 3 females, with an average age of 41.3±13.5 years), admitted to the Neurorehabilitation-Vegetative State Unit of the ASLCN1 in Cuneo ; all patients were in UWS or MCS for CVA (6 extensive brain hemorrhage), TBI (7 patients) and anoxic (3 patients). Patients did not presented associated spinal cord injury and were all having a value ≤ 3 on the Level of Cognitive Functioning (LCF) Scale[4]. The LCF, including the modified LCF-R version, is a "process scale", that is, it evaluates patient behaviour and thus the patient's cognitive level from the moment he or she goes into coma until recovery. It can functions as the instrument for patient evaluation across different units, e.g. it can also be used in the intensive care unit.

The Neurorehabilitation Unit accepts clinically stabilised patients with a diagnosis of traumatic brain injury or non-traumatic brain injury. The only criterion precluding access to the Unit is mechanical ventilation. Patients with a tracheotomy tube or percutaneous endoscopy gastrostomy (PEG) tube are accepted and there are no time limits with respect to the acute event, although the earliest possible access is guaranteed.

A detailed medical history was collected for all patients. A physical medicine examination and neurological examination were carried out every week to evaluate spasticity and, where necessary, radiological and neuroradiological investigations were carried out every month.

The rehabilitation programme for these patients includes the provision of optimal nutrition, control of infections, management of bladder, bowel and autonomic disorders, provision of specialist seating and control of posture and tone problems. Patients underwent one hour of physical therapy treatment and one hour of speech therapy every day, to prevent tertiary injury. Rehabilitative treatment involved passive joint mobilisation and helping/placing patients into an upright sitting position on a tilt table.

All the patients were evaluated upon entry as to their bladder and bowel voiding, combining clinical observations with items specific to related activities contained within the Functional Independence Measure (FIM).

IBT was proposed when severe spasticity became interfering with passive function, positioning or caregiving[5].

All patients were urodinamically evaluated before and one month after Baclofen pump implantation. During urodynamic study were evaluated the presence of Detrusor

Overactivity (DO), Maximum Cystometric Capacity (MCC), detrusor pressure at opening bladder neck (detrusor leak point pressure, DLPP) that coincide to detrusor pressure required to void.

In all patients were applied the Modified Ashworth Scale (MAS), separately for upper and lower limbs, and the Spasm Score, before and after implant, to evaluate changes in spasticity.

In all patients were evaluated Post Void Residual (PVR) pre and post IBT.

In 12 patients we performed a second urodynamic evaluation 6 months after implant, evaluating the same urodynamic findings (DO, MCC, DLPP).

Statistical analysis were performed using paired t-test and/or paired Wilcoxon test when appropriated to evaluate the difference in Ashworth and spasm scale, and to evaluate the urodynamic results at baseline and 1 and 6 months after IBT. We used Fisher's exact test to evaluate the number of patients in Clean Intermittent Catheterization (CIC), and the conscious state at baseline and after IBT. We considered statistical significant when p≤0,05.

RESULTS

Mean age of patients included in the study was 41.3±13.5 years, mean duration of UWS or MCS were 16.7±9.1 months, elapsed time between cerebral injury and our centre's admission was 149.5±41.5 days. At admission 3 patients were in MCS and 13 in a UWS. Time of catheterization was 117,9±98.4 days. At baseline all patients were in spontaneous micturition (reflex urinary incontinence); in 4 out of 16 patients CIC was necessary because high PVR.

Criteria for the implant were: MAS score 2 for three or more joints even if on the same body side; no signs of infection detected by a negative hemoculture, number of white globules in the normal range and absence of fever in the week before the implant.

In all patients we observed an improvement of spasticity, especially of lower limbs after IBT. The mean MAS preimplantation was 2.8±0.4 for upper limbs and 3.5±0.5 for lower limbs, spasm score was 1.8±0.7. After IBT MAS was reduced, 2.4±0.5 for upper limbs and 2.2±0.4 for lower limbs with a statistical significant difference (p≤0.01). Also Spasm Score was improved, after ITB measuring 1.5±0.5 with a significant statistical difference respect baseline (p≤0.03).

One month after IBT in 8 out of 16 patients was necessary CIC for high PVR (Fisher's exact test p≤0.27). Six months after implantation CIC was necessary in 3 out of 12 patients (Fisher's exact test p≤0.3).

At urodynamic evaluation mean baseline MCC was 364,6±150.1 ml., one month after IBT was 391.9±40.8 ml. (p≤0.03). Mean MCC six months after implant (12 patients) was 368.1±146.2 ml (p≤0.11). DLPP was 98.3±7.4 cmH_2O at baseline and 83.8±11.5 cmH_2O one month after IBT, with a significant statistical difference (p=0.04). in the 12 patients evaluated 6 months after IBT mean DLPP was 85,7±12.8 cmH_2O (p≤0.05 respect baseline).

Mean PVR at baseline was 57.5±21.7 ml., and 100.4±50.9 ml. one month after IBT (p≤0.01), although 6 months after IBT mean PVR was 56.8±24.5 (p≤0.58 respect baseline). At baseline in 10 out of 16 patients a DO was identified, after IBT DO was present in 3 out of 16 patients (p≤0.02), and in two patients 6 months after implant.

We observed an improvement in conscious state, at hospital admission 13 out of 16 patients were in VS and 3 out of 16 in MCS, at discharge 7 out 16 were in SV and 9 in MCS (Fisher's exact test p≤0.14).

TABLE 1. Demographics and clinical variables of the enrolled patients (n=16).

	n.	%
male	13	81.3%
female	3	18.7%
age (years±SD)	41.3±13.5	
Duration of DOC (UWS/MCS) prior to ITB (months±SD)	16.7±9.1	
Type of brain injury		
Traumatic	7	43.8%
Hemorragic	6	37.5%
Anoxic	3	18.7%
Indications for ITB treatment		
Severe Spastic Hypertonia	8	50%
Spastic Hypertonia and spasms	4	25%
Spastic Hypertonia and Dysautonomia	4	25%

TABLE 2. Urodynamic data before and after ITB.

	1-3 weeks after implant (T1) (n=16)			4-5 months after implant (T2) (n=12)		
	baseline	T1	p	baseline	T2	p
Detrusor Leak Point Pressure ($cm H_2O$)	98.3±7.4	73.8±11.5	0.043	98.3±7.4	83.8±14.9	0.152
Maximum Cystometric Capacity (ml.)	364.6±150.1	391.9±40.8	0.031	364.6±150.1	378.1±146.2	0.118
Detrusor Overactivity (yes)	7 (58.3%)	3 (25.0%)	0.045	7 (58.3%)	2 (16.7%)	0.025
Post-voiding Residual Urine Volume (ml.)	57.5 ± 21.7	100.4 ± 50.9	0.01	57.5 ± 21.7	56.8 ± 24.5	0.58

DISCUSSION

Penn and Kroin were the first to report good results with continuous IBT in patients with severe spinal spasticity. A dramatic clinical improvement was reported[6].

Spasticity of supraspinal origin is much more common than spinal spasticity, but treatment with ITB has been evaluated far less frequently in this condition[7]. Reports of successful treatment of patients with supraspinal spasticity are limited[8,9]. Especially patients with severe traumatic and/or hypoxic brain injury often suffer from severe tetraspasticity that is unresponsive to oral medication, physiotherapy or other antispastic therapies.

In the oral pharmacological approach to spasticity, baclofen, a γ-aminobutiryc acid (GABA) agonist, is often used, although in certain cases a lack of response, a ceiling effect or significant side effects as disorientation, dizziness, asthenia and ataxia are revealed when the useful dosage is reached.

The intrathecal administration through a programmable infusion pump system allows an effective control of spasticity after a serious brain lesion with fewer side effects than the oral treatment and with an important global functional improvement.

More limited are the reports on IBT use in patients in UWS or MCS.

Moreover IBT has been demonstrated to be effective to improve bladder capacity or to decrease sphincter dyssynergia in patients affected by spinal cord spasticity. Only a few reports have been published on ABI, especially on the

correlation of urodynamic findings, because injured patients commonly have behavioral, cognitive, or communication problems[10]. The injury to the brain itself, impairment of cognitive and behavioral function, may induce lower urinary tract symptoms (LUTS), as detrusor hyperactivity, only rarely associated with bladder-sphincter dyssynergia, and emptying phase disorders[11,12].

The most commonly expected urodynamic abnormality after ABI is involuntary detrusor contraction, which can be induced by the loss of cortical inhibition caused by suprapontine lesions. Coordinated relaxation of the distal sphincter during detrusor contraction is usually maintained. The incidence of urinary retention after ABI is lower than that after cerebrovascular accident (CVA). Very little is known about changes in urodynamic pattern in patients in UWS or MCS after ABI or CVA treated with ITB[13,14].

The use of baclofen is recommended in the treatment of LUTS thanks to two main modes of action:

– The inhibition of the hypertone which involves the external urethral sphincter

– The increase of detrusor compliance with subsequent increase of the bladder's filling capacity

The use of intrathecal baclofen in the patients suffering from disorder of consciousness is spreading more and more, and not only for the treatment of spasticity and neurovegetative crisis but also for the possibility to induce a change in positive of the state of consciousness, many are today reporting in this sense[15]. Another element to be reckoned with in clinical practice is the indication, suggested by some authors, to use early implant in order to prevent the impairment linked with spasticity before it is structured, thus making almost vain the only pharmacological or rehabilitative intervention.

In people affected by DOC as UWS or MCS, the good clinical practice suggests the weaning from an indwelling catheter because – except for prior problems or coexisting bladder issues – it is a case of overactive bladder emptying without bladder-sphincter dyssynergia. Therefore, it is important to know the potential risk of bladder overdistention due to urinary retention in patients implanted with a baclofen intrathecal release system.

This study, even considering the modest numerosity of the sample, allowed to verify that after the implantation of IBT a significant increase of MCC and a reduction of DLPP. Also the presence of DO is detected with a significantly reduced frequency respect baseline. Accordingly an increase in PVR in the first month was identified. While this data may seem a positive result of the therapy must be related to the type of patient treated, indeed the reduction of a detrusor contraction that it is not supported bysupraspinal centers can create an increase of the PVR. However, this discrepancy was filled out six months after implantation, and the PVR returns comparable to the baseline. Instead, positive results on the reduction of DO were maintained in the long term. The data therefore indicate the need to monitor PVR closely, in the first weeks after implantation, to avoid the risk of bladder supra-distension in these patients with disturbance of consciousness.

CONCLUSIONS

After IBT there was a significant increase of MCC and a reduction of DLPP. Accordingly, an increase in PVR in the first month was identified. While these results may seem a positive consequence of the therapy, they must be related to the type of patient treated, indeed the absence of a detrusor contraction supported by supraspinal centres can create an increase of the post-void residual. However, this discrepancy was filled out six months after implantation and the PVR returns comparable to the baseline.

The data observed would confirm the necessity of carefully monitoring, during the first weeks after the implantation, the likelihood of bladder overdistention in subjects with DOC whose bladder indwelling catheters have been removed and with an "automatic" micturition without bladder-sphincter dyssynergia. The monitoring (if possible with the use of bladder scans) should be prolonged for at least six months, when it seems conceivable the return to cystomanometric values which could be overlapped to the preimplantation ones.

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