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Research Article

Intrathecal Baclofen in Brain Injury and Recovery from Vegetative State

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2. Key words

BI (Brain Injury); Disorder of Consciousness (DOC); Intrathecal Baclofen Therapy (ITB); Permanent Vegetative State (PVS); Minimal Conscious State (MCS)

1. Abstract

Patients with brain injury (BI) and spasticity are candidates to Intrathecal Baclofen Therapy (ITB) when maximal dose of oral antispastic drugs fail. Some authors describe an improvement in the level of consciousness (LC) in patients with BI and Disorder of Consciousness (DOC) treated with ITB for spasticity.

We present the case report of a 43 years old patient with BI, spasticity and Permanent Vegetative State (PVS) lasting ten months, who showed an improvement in the LC after ITB indicated for spasticity management.

We performed ITB infusion test, assessing the spasticity with de Modified Ashworth Scale (MAS) and the LC with Coma Recovery Scale- Revised (CRS-R). We observed an improvement in the spasticity and the LC during the ITB Infusion Test. A few days after the test finished, the LC returned to the previous state. Due to the positive results, the intrathecal baclofen pump (IBP) was implanted. When the IBP was finally implanted, the patient recovered from PVS.

1.1. Conclusions: ITB is indicated in patients with BI and spasticity. We suggest the improvement in the LC as a possible added benefit, which could be a new indication for prescribing ITB in patients with BI and DOC. However, there is a lack of evidence to recommend it.

3. Introduction

Intrathecal Baclofen Therapy (ITB) is indicated for the treatment of spasticity and dysautonomy in patients with spinal or Brain Injury (BI) [1] when the maximal doses of oral antispastic and injections of BotulineToxine A fail in the purpose or the subjects do not tolerate the side effects of oral antispastic drugs. In patients with severe BI and Disorder of Consciousness (DOC), the first indication for ITB is in the management of spasticity. The main objective of ITB is a functional outcome for better positioning, easier hygiene and less pain.

Baclofen is a Gaba Amino-butyric acid (GABA) agonist that acts activating the GABA-B receptors in the presynaptic neuron in the pyramidal pathway. GABA is an inhibitory neurotransmitter in the Central Nervous System that is implicated in the control of excitatory stimuli by Glutamate. In normal situation there is a balance between both, glutamate and GABA, that allows a correct motor function [2]. There is a theoretical model that describes the situation in the brain after Traumatic Brain Injury. In this model, there is an impaired GABA-B receptor. Due to that, GABA doesn't trigger the normal inhibitory response. As a consequence, there is an imbalance between glutamate and GABA resulting in an excess of excitatory response [2].

Some authors have described an improvement in the Level of Consciousness (LC), besides the decrease of the spasticity, in patients with severe BI with also DOC after ITB pump implantation [3-8]. The first case reported was in 2007 by Sarà et al. [4]. who described a case of a 44 years old man with nontraumatic BI and Minimal Conscious State (MCS) to whom an ITB pump was implanted 11 months after the injury for spasticity. From a dose of 100mcg/day they described an improvement

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in the LC without any scale referred. In 2009, the same group published a new article [3]. They followed up 5 patients with BI and DOC, due to different causes (Subarachnoid Hemorrhage-SAH, Traumatic Brain Injury-TBI, hemorrhagic stroke and post anoxic encephalopathy). The ITB pump were implanted in a mean of 9.2 months after injury and they scored the LC with the Coma Recovery Scale Revised (CRS-R) during 6 months after implantation of ITB pump. All except one of them improved the LC. In 2010, two more cases were reported [5], both in patients with SAH, spasticity and DOC. The improvement in the LC was related with the description of actions they could carry out and the Coma Glasgow Scale (CGS). In one of them, the ITB pump was implanted in the second month after the onset of SAH. Xavier Hoarau et al. [9]. published a 10 years follow-up study with patients with BI to whom the ITB pump was implanted for the treatment of spasticity and disautonomy. At the end of the follow-up they made a retrospective analysis reporting the LC according to GCS at admission and they compare with the LC at the end of the follow up with the CRS-R. They correlate the information at admission and at the end of the follow-up, without clear conclusions about the possible effect of IB in the LC. In 2013, Konstantinos Margetis et al. [8]. published a 2 years follow-up study of 8 patients with BI (TBI, Anoxic injury and hydrocephalus), spasticity and DOC. The ITB pump was implanted in a mean of 37.25 months after injury. They reported the LC with the CRS-R but their results were very different to the study of Sarà et al. [3] perhaps, they say, because of the different characteristics of the cohorts. In 2015, two more case reports were published by A.T. Al-Khodairy et al. [6]. They reported two patients with Traumatic Brain Injury, DOC and spasticity. They placed the ITB pump and described an improvement in the LC, first reported by the CRS-R and finally reported according to the cognitive items of the Functional Independence Measurment (FIM). The last case report in the literature occurs in 2015 [7]. In this case Asahi T. introduced a new concept: temporary beneficial effect in the ITB after BI in the first 2 months after onset to accelerate the improvement in the LC and spasticity.

In seven years, 18 case reports of patients with BI and DOC treated with ITB for spasticity have been published. Despite that, there is not enough evidence to recommend the ITB in patients with BI and DOC.

We present a new case of a patient with severe non traumatic BI who was treated with ITB for spasticity and experimented also an unexpected improvement in the level of consciousness.

4. Case Report

A 43 years old woman was admitted to our Neurorehabilitation Hospital in January 2016 with the diagnosis of spastic tetraparesis and PVS. The patient suffered anhaemoragic stroke in July 2015 due to the ruptured of an aneurysm in the intracraneal internal right carotide. She was admitted in the Intensive Care Unit (ICU) of her hospital with IntracranealHipertension needing a bifrontalcraniectomy. A long stay in the ICU required tracheostomy and percutaneous gastrostomy. After 6 months with the diagnosis of Vegetative State and spastic tetraparesia, the patient was admitted in our center.

The patient had a spastic tetraparesia scored with Modified Ashworth Scale (MAS) of 4 in all limbs and claw hands. It was very difficult to do the diary hygiene and to keep her properly positioned in the wheelchair. We administrated her oral baclofen (35mg/8hours) and tizanidine (6mg/8 hours) without improvement of the spasticity. ToxBot A was inyected in the flexors fingers bilateral without satisfactory outcome.

The LC was very low, scored with the CRS-R with a first punctuation of 5 in the 8th month after onset (17th March 2016). She had intermittent periods of wakefulness and no sign of self or environmental awareness.

She received diary cognitive, sensorial stimulation and physiotherapy since her admission. Modafinilo was introduced to improve the LC in the 9th month after injury (4th April 2016). Four days later, the evaluation with the CRS-R scored 8 (improving visual function and awareness in comparison with the first CRS-R evaluation few weeks before) (Table 1).

Apart of the LC and also in the 9th month after onset, we de-cided to do an ITB test, due to the uncontrolled spasticity with highest dose of oral antispastics. One first intrathecal bolus of 50mcg was injected with no decreased spasticity. The second bolus of 100mcg also failed to improve spasticity. Some days later, in the same month (26th April 2016), we proceed to do a one week progressively continuous infusion of ITB through an external catheter placed in the intrathecal space. With a dose of 800mcg/day the spasticity decreased to MAS 3. Unexpectedly, we also observed important cognitive changes. The patient started to obey simple commands, to move the right arm with intention (to take a bottle of water to the command), recognizing people, saying their names and answering simple questions. No CRS-R was applied in this phase. After the catheter was removed, the patient returned to her previous state in a few days. After these outcomes, we decided to place a definitive ITB pump. It had to be delayed due to the clinical situation of the patient to July 2016 (11 months after onset). The dose of oral baclofen and tizani-dine were progressively decreased at the time the ITB dose was increased. With a dose of 920mcg/day in continuous mode, we observed the expected decreased spasticity to MAS 3. About the cognitive state, we observed similar outcomes as in the test, with

intentional actions and words emission, but not as consistent as observed before. The CRS-R after ITB pump implantation (on 9th June 2016) was 13, that meant the recovery from PVS to MCS (**Figure 1**). The summary of LOC evaluation can be seen in the (**Table 1**).

Table 1: CRS-R score during the follow-up.

CRS-R	17/03/2016 8th month after onset	04/04/2016 9th month after onset	09/06/2016 11th month after onset
Auditive function	1	1	4
Visual Function	0	1	2
Motor Function	2	2	2
Verbal Function	1	1	2
Communication	0	0	1
Awareness level	1	3	2
TOTAL	5	8	13

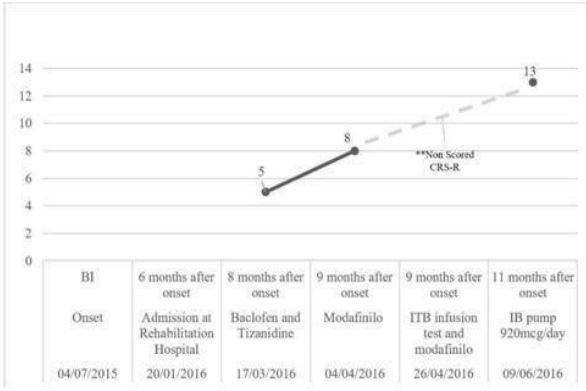

Figure 1: CRS-R score during the follow-up and treatments administrated.

The initial objectives for easier caring, better positioning and less pain were reached. The LC was also higher, according to the outcomes described but, unfortunately, not as consistent as we expected after the initial test. At discharge, the infusion mode was changed to flexible mode (120mcg/day plus 200mcg bolus every 6 hours) to optimize the beneficial effect for the patient. We think her cognitive achievement is fluctuant depending on the clinical and environmental situation. Despite that, we can affirm that after ITB, there was a significant improvement in the LC and cognitive achievements, independently of modafinilo administration; as well as the expected decreased in the spasticity that allows her careers to manage the situation easier.

5. Discussion

We report a new case in which a patient with non-traumatic BI recovers from PVS to MCS after the introduction of ITB for spasticity. Although we introduced modafinilo before ITB, we didn't observed clinical relevant results until we made the ITB infusion test. We observed, as well as the improvement in the spasticity, important cognitive changes. Unfortunately, we didn't apply the CRS-R at this time. These changes can be explained because of the introduction ofITB, considering that the modafinilo was present before the beginning of the ITB administration and the improvement in the LC was more significant after ITB infusion test. Even the modafinilo was kept during later months, and the LC did not reach so good results as we saw initially. Due to these facts, we can attribute the improvement in the LC to ITB.

We lay out the method to objectivize the LC. In all the reports and articles published there is not homogeneous way to evaluate de LC. Glasgow Coma Scale (GCS), Cognitive items of the FIM and CRS-R are used in the case reports and are compared between them. Most of the author use the descriptions of actions performed to objectify the LC. The GSC doesn't allow the distinction between PVS and MCS [10]. The FIM is an instrument that assesses in the patient disability and functional improvement [11, 12]. Only the CRS-R is the Gold Standard for the differentiation of PVS and MCS, and also allows the detection of the emergence from MCS [10]. Unfortunately, we could not apply the CRS-R test at the time we observed more cognitive changes. As most of the authors, we had to use the descriptions of actions performed to objectify the improvement in LC at the time we observed greater cognitive improvement, but also the CRS-R was performed in most of the evaluations. In that way, we could objectify the recovery from PVS to MCS.

Few hypothesis have been suggested to explain the mechanism of ITB in the LC without a clear explanation Sarà et al. [3]. propone that the impaired proprioception caused by the brain injury and the muscles spasticity might affect negatively in the maintenance of consciousness in an injured brain [3,4], based on the study of Motokizawa F. in rats, that showed that tonic sensory and muscle-sprinde activity modulate cerebral activity and wakefulness [13]. Baclofen may modulate the sensitive information reaching the cortex [3,4,8]. Reducing the oral baclofen may also affect in the improvement of the LC[3,4], what is also the situation in our patient. A paradoxical effect of ITB in patients with special clinical situation or genetic polymorphism in the receptors and transporters of GABA have been also hypothesized Sarà et al. [3]. Low dose of baclofen has been said to produce an amphetamine endogenous like effect [5,14]. ITB might have effects on serotonin release and alertness [8,15]. Taira et al. postulated that ITB might improve the axonal conduction in injured neurons [8,16]. ITB might also modulate GABA-B receptors in the orexin pathway in the lateral hypothalamic area, implicated in the sleep/wake states [8,17,18]. Another theory says that the effect of ITB is located in the Thalamic reticular nucleus facilitating the attentional processes. This neurons are injured very frequently in the BI[8,19-23]. ITB may help to restore the altered cortical networks restoring the inhibitory neurotransmission [2,24, 25].

We discuss the effect of ITB in the LC: does it depend directly on the effect of baclofen in the neurons or does the reduction of spasticity allow the patients to perform better in the CRS-R?

In that way, there are some hypotheses suggested[26]. Also, we present new questions: does the LC depend on the ITB or on the reduction of adverse secondary effects due to highest dose of oral baclofen?

We don't have clear arguments to support the indication of ITB for improving the LC in patients with BI, although it has been reported in many studies that ITB may have an important role in the partial or complete recovery of PVS to MCS [8,27]. Further studies with control group must be done to clarify the direct effect of ITB in the LC in patients with BI and to explain the direct effect of ITB in the LC.

In conclusion, ITB is indicated for the treatment of spasticity in spinal cord and BI when maximal dose of oral antispastic drugs are ineffective or adverse secondary effects are present. Some patients with severe BI, spasticity and DOC, have been treated with ITB for the management of spasticity. An improvement in the LC after ITB, apart of the decrease of the spasticity, has been described. We report a new case of a patient in PVS due to non-traumatic BI, who reached MCS after the introduction of ITB for the treatment of spasticity. There is not enough evidence to rec-ommend ITB to improve the LC in patients with BI because all the evidence is based on case reports and observational studies. Further studies must be done, but every new point can lighten the way to understand better the behavior of consciousness and can give the patients a new chance for more quality of life.

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