Intrathecal Baclofen Infusion Pumps in the Treatment of Spasticity: A Retrospective Cohort Study in a Portuguese Centre

Bombas Perfusoras de Baclofeno Intratecal no Tratamento da Espasticidade: Estudo de Coorte Retrospetivo num Centro Português

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ABSTRACT

Introduction: Spasticity is a complex problem in patients with neurological disorders and may distress their quality of life. Intrathecal baclofen infusion pumps reduce spasticity with low doses and minimal side effects but are not free from complications. We aimed to evaluate the efficacy and safety of intrathecal baclofen infusion pumps as well as patients' satisfaction.

Material and Methods: Retrospective cohort study including all intrathecal baclofen infusion pumps placed up to December 2015. Demographic characteristics, clinical diagnoses, date of placement or withdrawal/replacement of intrathecal baclofen infusion pumps, baclofen dosage and complications of intrathecal baclofen infusion pumps were collected. Assessments from the Ashworth and Penn's scales, Katz index and patients' global satisfaction were analysed.

Results: In 19 years we placed 251 intrathecal baclofen infusion pumps in 155 patients. The mean age was 41.1 ± 15.8 years. The most frequent conditions were: trauma (34%), cerebral palsy (14%), multiple sclerosis (12%) and stroke (12%). Eighty-five patients (55%) required a second pump, and eleven (7%) a third one. The lifetime of the first pump was 72 (36 – 89) and the total follow-up time was 96 (9 – 132) months. The causes of withdrawal/replacement were: battery failure (57%), catheter migration/kinking (24%), infection (14%) and pump displacement/exteriorization (7%). The complication rate was 0.21 events/month. There was a significant improvement in the Ashworth and Penn's scales after the placemen of intrathecal baclofen infusion pumps ($p < 0.001$ for all diagnoses) and the patients were satisfied with the treatment.

Discussion: The incidence of complications was within range of other international studies despite our long follow-up time. Events per month, loss to follow-up, re-intervention rate, incidence of infection and mortality were similar to other studies.

Conclusion: Intrathecal baclofen infusion pumps are safe and effective in the treatment of spasticity. Infusion pumps provide a high level of satisfaction regarding treatment and quality of life.

Keywords: Baclofen/administration & dosage; Baclofen/therapeutic use; Infusion Pumps, Implantable; Muscle Spasticity/drug therapy

RESUMO

Introdução: A espasticidade é um problema complexo em doentes com distúrbios neurológicos influenciando a sua qualidade de vida. As bombas perfusoras intratecais de baclofeno reduzem a espasticidade com doses baixas e efeitos laterais mínimos, mas não estão livres de complicações. Pretendemos avaliar a eficácia, segurança e satisfação dos doentes com bombas perfusoras intratecais de baclofeno.

Material e Métodos: Estudo de coorte retrospetivo, incluindo todas as bombas perfusoras intratecais de baclofeno colocadas até dezembro de 2015. Foram avaliadas as características demográficas, diagnósticos, data de colocação ou retirada/substituição e complicações das bombas perfusoras intratecais de baclofeno. Analisaram-se as escalas Ashworth, Penn, Katz e satisfação dos doentes.

Resultados: Durante 19 anos colocaram-se 251 bombas perfusoras intratecais de baclofeno em 155 doentes. A idade média foi 41,1 ± 15,8 anos. As patologias mais freqüentes foram: traumatismo (34%), paralisia cerebral (14%), esclerose múltipla (12%) e acidente vascular cerebral (12%). Oitenta e cinco doentes (55%) precisaram de uma segunda e onze (7%) de uma terceira bomba. A semi-vida da primeira bomba foi 72 (36 – 89) e o tempo total de seguimento 96 (9 – 132) meses. As causas de retirada/substituição foram: falha de bateria (57%), migração/*kinking* do cateter (24%), infeção (14%) e deslocamento/exteriorização da bomba (7%). A taxa de complicações foi 0,21 eventos/mês. Houve uma melhoria significativa nas escalas de Ashworth e Penn após colocação das bombas perfusoras intratecais de baclofeno ($p < 0,001$ para todos os diagnósticos) e os doentes ficaram satisfeitos com o tratamento.

Discussão: A incidência de complicações situou-se dentro do intervalo reportado por outros estudos internacionais, apesar do longo tempo de seguimento. Número de eventos por mês, perda de seguimento, taxas de re-intervenção ou infecção e mortalidade foram semelhantes a outros estudos.

Conclusão: As bombas perfusoras intratecais de baclofeno são seguras e eficazes no tratamento da espasticidade e oferecem um alto nível de satisfação quanto ao tratamento e qualidade de vida.

Palavras-chave: Baclofeno/administração e dosagem; Baclofen/uso terapêutico; Bombas de Infusão Implantáveis; Espasticidade Muscular/tratamento

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INTRODUCTION

Spasticity is a complex problem that follows an upper motor neuron injury, affecting muscle tone and resistance to passive stretch, and is associated with hyperreflexia and muscle spasms.[1] It is a consequence of numerous conditions of the central nervous system (CNS) such as traumatic brain injury (TBI), spinal cord injury (SCI), stroke, cerebral palsy (CP) and multiple sclerosis (MS).[1] Spasticity may cause pain, discomfort and interfere with mobility. In addition to the physical consequences, patients often present emotional disturbances and may become dependent, which affects their quality of life.[1]

Various functional scales classify the severity of the disease. The Katz Index grades the patient as independent, partially dependent, and totally dependent, depending on the activities that can be accomplished before any treatment. The Ashworth and Modified Ashworth scales are based on the degree of muscle tone assessment while the Penn Scale is based on the frequency of muscle spasms. These scales range from 0 to 4 in accordance to the presence of more or less tonus or muscular spasms. These quantitative scales are not only used to assess the degree of spasticity, but also to evaluate treatment efficacy.[2–17]

Baclofen acts on γ-Aminobutyric acid (GABA)-B receptors inhibiting the release of excitatory neurotransmitters and reducing spasticity. As a result of its low lipid solubility, oral baclofen barely crosses the blood brain barrier. Intrathecal administration reduces muscle tone with only 1% of the oral dose being required. A continuous administration is desirable as its half-life in cerebrospinal fluid (CSF) is only five hours and has limited dispersion.[1] This is accomplished with infusion pumps (IPs) which have two components: a refillable reservoir connected to an intrathecal catheter and a lithium battery. The infusion rate and additional boluses can be programmed externally by radio telemetry. Before the placement of IPs, a test dose is performed with 50 or 100 µg of intrathecal baclofen, followed by spasticity evaluation every 2 hours for 6 – 8 hours. The test is positive if there is a 2 point reduction in the Ashworth or Modified Ashworth scale.[2–18]

Possible complications of IPs are surgical (infection, dehiscence); intrinsic pump failure (mechanical or battery failure, migration, occlusion, fracture or disconnection of the catheter); and human error (overdoses by mistake while programming doses or pump refills). These can lead to discontinuation of therapy, surgical removal of the pump, or, in rare cases, death. Prolonged administration causes down-regulation of receptors and the abrupt discontinuation may lead to withdrawal syndrome. Alarms decreased human errors and improved detection of mechanical problems. Technological evolution allowed its use in paediatric patients.[6,10,16,19–22]

Our Chronic Pain unit (CPU) is a national reference in the treatment of patients with spasticity. This study aimed to evaluate the efficacy and safety of IPs, their complications, as well as the patients' satisfaction with this treatment.

MATERIAL AND METHODS

Retrospective cohort study approved by the institutional ethics committee of our hospital including all patients with an implanted IP since 1997 until December 2015. Demographic characteristics, clinical diagnoses, date of placement or withdrawal/replacement of IPs and baclofen dosage in micrograms /day were collected. Assessments from the Ashworth and Penn's scales pre and post placement of IPs, Katz Index and patients' global satisfaction (numeric rating scale from 0 to 10, 0 being very unsatisfied and 10 totally satisfied) were also analysed. All complications related to the IPs or intrathecal catheter were obtained until December 2015.

The histogram and the Kolmogorov-Smirnov tests were used to evaluate the distribution of ordinal and continuous variables. A descriptive analysis was used to summarize the results with the data being presented as mean ± standard deviation (SD) or median and interquartile range (P25-P75). Dichotomic variables were analysed with the X^2 or Fisher tests and the continuous variables were analysed with the Mann-Whitney test, paired or independent *t*-test. A statistically significant p was defined as < 0.05.

RESULTS

In a total of 19 years (1997 – 2015), 251 IPs were placed in 155 patients, thus averaging 14 pumps per year. Table 1 presents patients' characteristics. The mean age was 41.1 ± 15.8 years, ranging from 7 to 77 years, with 14 patients (9%) under 18 years old. There were no differences in age between genders ($p = 0.79$). The most frequent condition was trauma (TBI or SCI) with 34%, followed by CP with 14%, MS and stroke both with 12%. The distribution of ages by clinical diagnoses is shown in Fig. 1. There was a

Table 1 – Patients' characteristics

	Total (n = 155)
Gender – n (%)	
– Male	105 (68)
– Female	50 (32)
Age (years) – mean ± standard deviation	41.1 ± 15.8
Clinical diagnosis – n (%)	
– Trauma	53 (34)
– Cerebral palsy	22 (14)
– Multiple sclerosis	19 (12)
– Stroke-related	19 (12)
– Neurodegenerative	15 (10)
– Inflammatory / Infectious	14 (9)
– Other	13 (8)
Pump replacements – n (%)	
– Once	85 (55)
– Twice	11 (7)
Pump withdrawal without replacement – n (%)	15 (10)
Follow-up time (months) – median (P25 – P75)	96 (9 – 132)
Lifetime of 1st pump (months) – median (P25 – P75)	72 (36 – 89)
Intrathecal baclofen dose (µg/day) – median (P25 – P75)	230 (95 – 400)

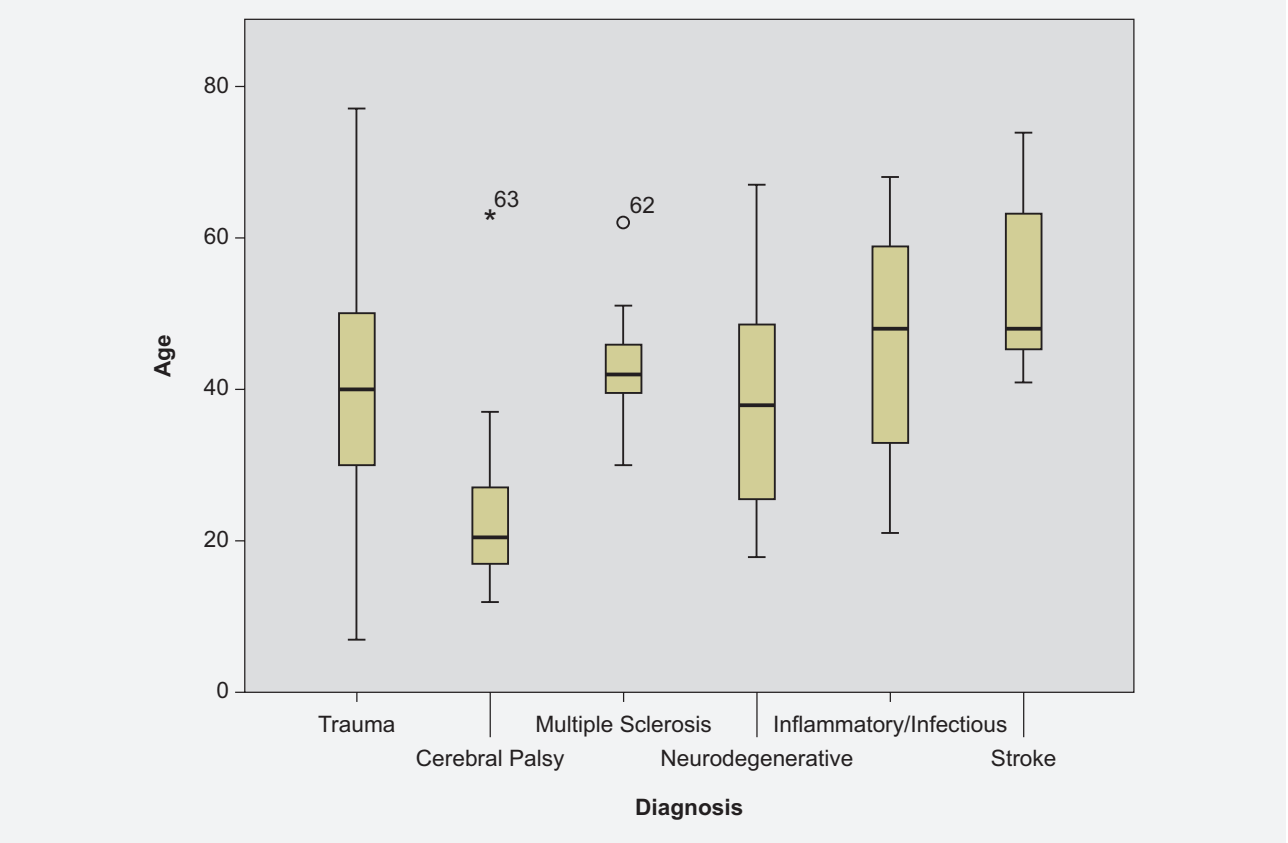

Figure 1 – Distribution of ages by diagnoses

statistically significant difference in age among patients with CP *versus* stroke ($p < 0.001$).

The invasive procedures of our CPU are performed in an operating room on a monthly basis, with patients being admitted the day before surgery. Our surgical team always includes two anaesthesiologists. Most pumps are placed under general anaesthesia. Antibiotic prophylaxis consists of intravenous cefazolin according to the institutional protocol.

A small incision between lumbar spinal processes, usually the L3 – L4 interspace, is made and the subarachnoid space is punctured with a 14G Tuohy needle, through which the guide wire catheter is introduced and advanced under radiological control until the T10 level. After removing the guide wire and with the catheter in the desired location, the needle is withdrawn. The catheter is then tunnelled subcutaneously from the lumbar region to the abdominal wall and connected to the IP when fully filled by CSF. It is fixed to the paravertebral muscles with a tense U-point to reduce the risk of CSF leakage. We used the Medtronic SyncroMed EL up to 2005 and SyncroMed II thereafter. The InDura intrathecal catheter (Model 8709SC) was used up to 2011, and was replaced by the Ascenda intrathecal catheter (Model 8780 – 8781) thereafter.

The starting dose of baclofen infusion is 50 µg/day except in paediatric patients where it starts at 25 µg/day. During postoperative hospitalization, the patient is re-evaluated daily and the dose is adjusted according to their spasticity. Subsequently, the patient is also re-assessed from time to time in the Outpatient Clinic, as well as during the pump refills. Continuous infusion with fixed dose is prescribed, total daily dose being 230 (95 – 400) µg/day, with a minimum dose of 25 and a maximum dose of 2130 µg/day.

During the follow-up period (1997 – 2015), 55% (n = 85) required a second and 7% (n = 11) a third IP. In 15 patients (10%) the IP was removed without replacement. The longevity of the patients' first pump was 72 (36 – 89) with a maximum of 144 months. The average follow-up time was 96 (9 – 132) months. Table 2 and Fig. 2 show the causes of withdrawal or replacement of the IPs, as well as the follow-up time until complications.

Excluding battery replacements that required interventions within the predicted time, there was a total of 48 complications in 251 procedures (an incidence of 19%). Dividing

Table 2 – Causes of pump withdrawal or replacement and follow-up time until complications

	Total (n = 111)
Reason for withdrawal / replacement	n (%)
– Battery	63 (57)
– Catheter (migration or kinking)	24 (22)
– Infection	16 (14)
– Pump displacement / exteriorization	8 (7)
Months until battery replacement – median (P25 – P75)	84.5 (81 – 102)
Months until infection – median (P25 – P75)	49 (13 – 78)
Months until catheter / pump complications – median (P25 – P75)	70.5 (15 – 86)

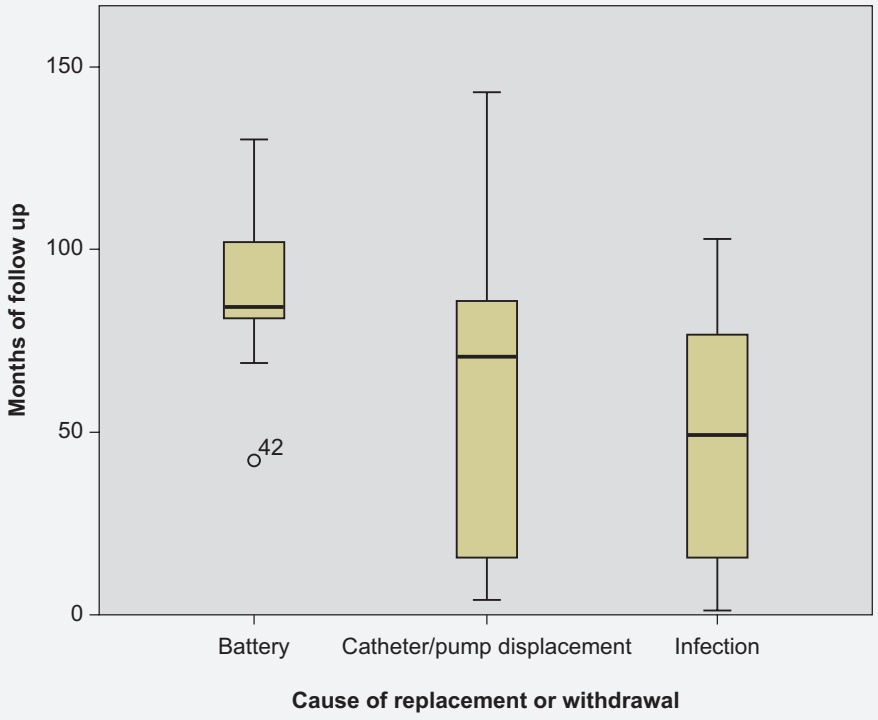

Figure 2 – Follow-up time up to the first complication in months

the number of complications by the number of months of follow-up (228), we found a rate of 0.21 events per month. Three rare events occurred: one CSF fistula demanding blood patch, one pump rotation inside a surgical pocket requiring relocation, and one abrupt baclofen withdrawal syndrome due to a catheter problem. It should be noted that the fistula event was prior to the insertion of the U-point for catheter fixation.

There were 10 patients lost to follow-up (6%) and 22 deaths (14%) from non-related causes. These patients were not different from all the others in terms of age, gender, pre-operative diagnoses, complications or follow-up time. No patient had any side effects directly due to intrathecal use of baclofen or neurological deficits as a result of this treatment.

We measured the pre-operative Katz Index in 107 patients, and 43% (n = 46) were totally dependent, 39% (n = 42) partially dependent and 18% (n = 19) independent. There were no significant differences in age, sex and diagnoses between groups. Regarding the Ashworth and Penn functional scales, there was a significant improvement comparing the pre [Ash and Penn 4 (3 – 4)] to the postoperative [Ash 1 (1 – 2) and Penn 1 (0 – 1)], $p < 0.001$ for all subgroups of diagnoses (Fig. 3). All of them were satisfied with the treatment (score ≥ 5), as shown in Fig. 4.

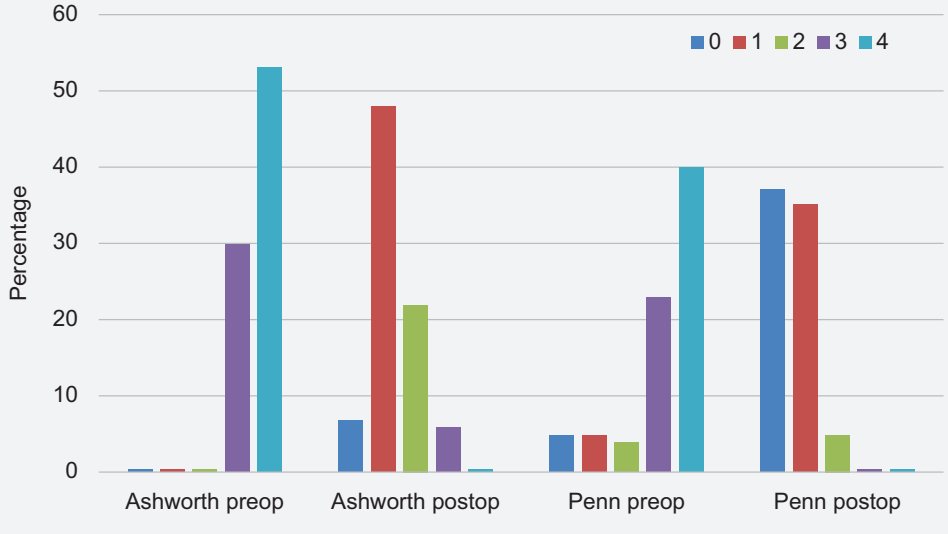

Figure 3 – Variation of the Ashworth and Penn functional scales between preoperative (preop) and postoperative period (postop), $p < 0.001$

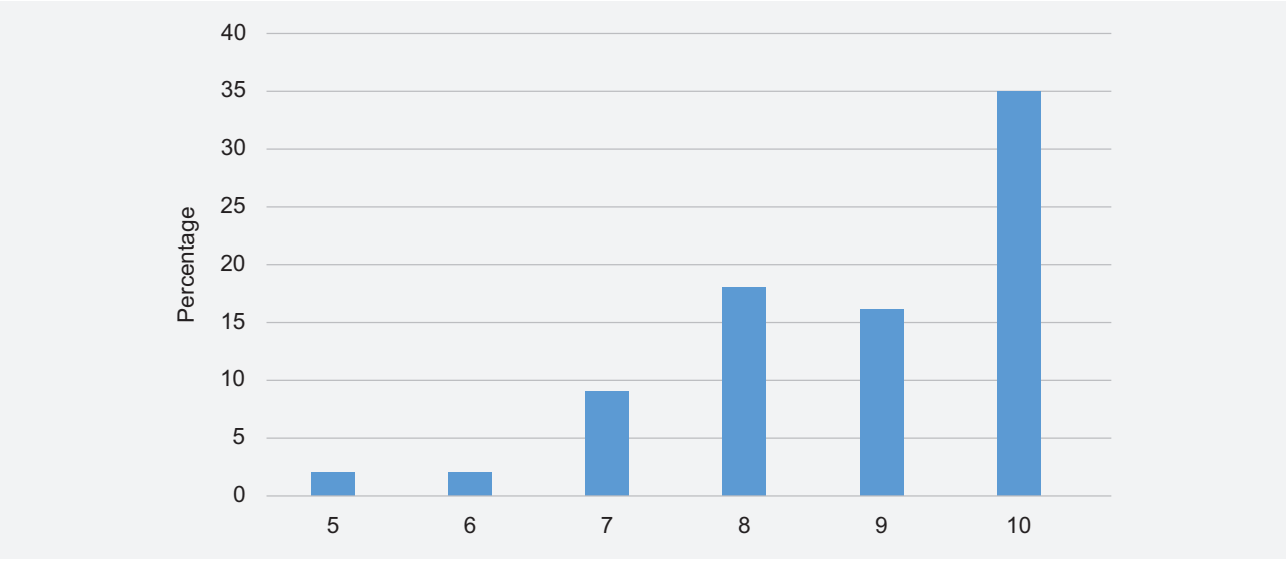

Figure 4 – Global patient satisfaction with the treatment (1 – 10). All patients were satisfied with the treatment (all answers ≥ 5).

DISCUSSION

During the 19 years of follow-up, 19% of procedures had complications (48/251). In other studies, the incidence of serious complications that required re-intervention varied between 25% and 37%, despite shorter follow-up times.[20–23] We had an average of 0.21 events per month, very similar to the 0.23 obtained by Borrini *et al*.[19]

According to Taira *et al*, the incidence of infection can vary between 0.8% and 15%.[22] We obtained an infection rate of 6.4% (16/251), less than the 26% of Borrini *et al*.[19] In the Motta *et al* study, carried out in a paediatric population, the subfascial implantation had a lower rate of infection compared with subcutaneous implantation: 3.6 *vs* 20.1%, $p < 0.001$.[21] Globally, the rate of infection in that study was 9.3%.[21] Some other studies[1] mention a higher rate of infection in patients with CP, which was not the case in our study ($X^2 = 0.703$, $p = 0.402$). Although the subfascial technique appears to have a lower rate of complications such as dehiscence or infections in the literature, we found a rate that is lower compared to most of those studies.[21] Type of infection, pathogenic agent and established treatment were already described by Malheiro *et al* regarding complications that occurred until May 2014.[24] Antibiotic prophylaxis with 2 g of intravenous cefazolin is recommended by national and institutional guidelines for surgical site infection prevention and may explain our results.[25]

Problems related to the catheter occurred in 9.6% of cases (24/251). In a summarized chart from Taira *et al*, we can see rates as different as 6% to 75%.[22] Before 2011, with first generation catheters, the study of its correct positioning or functioning could be done by simple radiography since it was radiopaque and there were those who defended periodic imaging as a way to detect early problems.[21] Currently, the new generation catheters are incompressible (anti-kinking system), but not radiopaque, requiring magnetic resonance evaluation. For this reason, at the time of placement, it is necessary to maintain the guide wire inside the catheter to allow its intraoperative visualization with fluoroscopy. When the catheter reaches the desired level, the guide wire is removed, as well as the needle.[18]

In our study, 22 patients died during the follow-up period corresponding to a mortality rate of 14%. In literature, this rate varies between 0 and 21%.[18,20,21,26] This difference can be explained by the inclusion of different conditions and different follow-up times.

According to Albright *et al*, teams dedicated to IPs must carry out a minimum of 10 annual procedures to maintain their skills.[22] In our CPU, we perform an average of 14 procedures per year. The 6% loss to follow-up is essentially due to patients changing address. We follow IPs implanted in our and in other medical centres in Europe.

Like in other investigations, this study demonstrated the efficacy of IPs in the treatment of spasticity, through the improvement of muscular tonus and the number of spasms.[2,7,14,15,20] The reduction of the Ashworth and Penn scales from pre to post-surgery was respectively 2 (2 – 3) and 3 (2 – 3), $p < 0.001$ for both, in line with the literature. This reduction was statistically significant in all the diagnostic subgroups with $p < 0.001$.

This study also tried to measure the therapeutic impact of IPs in the quality of life using a global satisfaction index. All patients confirmed improvements with the IPs (≥ 5 score) and almost half (44.6%) rated their quality of life and everyday activities with the level 10. It should be noted that 84% presented a level of satisfaction ≥ 8, similar to the study of Mathur *et al*.[2]

Most patients showed a therapeutic control with a dose of 230 (95 – 400) µg/day of baclofen. These doses are similar to those described in the literature.[2–5,7,9,11–17,19,22,26–29]

The cost-benefit analysis carried out by Saulino *et al* demonstrated a high initial cost with the IPs but with mitigation and even long-term benefit.[30] The transition from a higher cost to a lower one would be around the second year after implantation, which corresponds in our study to

a significant benefit since the follow-up time is long (median of 96 months). It is expected that the improvement in physical and mental well-being of patients promotes a lower number of complications, such as pressure sores or venous thrombosis, leading to a lower number of hospitalizations, thus making IPs cost-efficient.

The limitations of our study are related to the fact that it is retrospective and only focuses on major complications that required surgical intervention. It was not possible to verify the existence of adjuvant therapies in the treatment of spasticity, such as physical therapy, orthosis or other drugs that can influence outcomes. It would be interesting to evaluate its efficacy in different muscular groups, such as upper and lower limbs but we did not have that data available for analysis.

CONCLUSION

The results of this study demonstrate that IPs are a safe, valid and effective therapy in the treatment of spasticity. Infusion pumps provide a high level of satisfaction in relation to the type of treatment and the patient's quality of life.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

All authors contributed to the study and declare no conflicts of interest.

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