Positive experience with intrathecal baclofen treatment in children with severe cerebral palsy

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ABSTRACT

INTRODUCTION: Treatment of severe spasticity and dystonia with intrathecal baclofen (ITB) in children has been shown to be effective and has therefore been employed in the Region of Southern Denmark. The aim of this retrospective study was to analyse the efficacy and adverse events since ITB was introduced in 2003.

METHODS: A total of 46 children who had a baclofen pump from April 2003 to January 2013 were included. The children's medical records were reviewed and clinical characteristics, efficacy and adverse events were registered. The efficacy of treatment experienced by parents was ascertained by telephone interviews, and data were rated on a Likert scale ranging from one to five, where one was no effect and five was marked improvement.

RESULTS: After ITB, spasticity was reduced from a median of four to two in the upper extremities and from a median of four to one in the lower extremities. Baclofen infusion was 105.1-2,000 micrograms/day (mean 494.9 micrograms/day). Oral baclofen was reduced from 27.3 to 17.7 mg/day after ITB ($p < 0.01$). The parents' assessment of improvement in well-being, function and ease of care of their child had a mean score of 3.7, 2.2 and 3.4, respectively. 87.1% of parents stated that ITB had been worthwhile, and 90.3% would recommend it to other parents. Most infectious and mechanical adverse events were experienced during the first 200 days after pump implantation. The total complication rate was 0.40 per pump year.

CONCLUSION: ITB resulted in reduced spasticity in children with severe spasticity and dystonia, and ITB could be considered safe. Parents' satisfaction with ITB was rated as good and most parents would recommend ITB to others.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Cerebral palsy (CP) is diagnosed with an incidence of between 1.5 and 2 per 1,000 live births in Denmark and is often predominated by spasticity [1]. Management of spasticity with intrathecal baclofen (ITB) was introduced by Penn and Kroin in 1984; and Narayan first described ITB use in dystonia in 1991. Baclofen is a GABA receptor agonist and binds presynaptic GABAb receptors, thus inhibiting neurotransmitter release to motor neurons in the spinal cord. Oral baclofen crosses the blood brain barrier poorly and needs to be administered in doses that often result in adverse events. ITB is administered in doses approximately 500-1,000 times lower than those taken orally [2]. Treatment with ITB has been shown to yield a significant reduction of spasticity in children [3-7].

The aim of this retrospective study was to investigate the effect of ITB and to evaluate adverse events in a Southern Danish cohort of paediatric patients treated in the period between April 2003 and January 2013. Qualitative data were collected through June 2014 for the children who are still associated with Region of Southern Denmark (RDS).

METHODS

Procedures

A total of 46 paediatric patients who were between 0-18 years of age at pump implantation were included. Approximately 7% of children with CP in RDS are treated with ITB. Before referral to ITB treatment, children were tested with 40-100 micrograms of baclofen intrathecally via a lumbar puncture procedure. A modified Ashworth score (MAS) was measured before and after the test. If the test was considered positive, then the MAS score was reduced by at least one point, the child could have a pump implanted and was referred for operation following parental consent. Each operation was performed in general anaesthesia, and antibiotics were administered preoperatively. First, by way of a dural puncture at level L2-4, the catheter was inserted intrathecally. The catheter was then cannulated subcutaneously to one side of the abdomen and connected to the pump, then placed in a subcutaneous pocket. Two different pump types were used; either a pressure-driven pump (volume 20 or 35 ml) or an electric pump (volume 20 or 40 ml). In August 2009, electric pumps were introduced. All patients who had a pump implanted after that year received an electric pump.

Data collection

Medical records were systematically reviewed and information gathered on operation data and clinical characteristics, including Gross Motor Function Classification System (GMFCS) scores [8] and MAS [9] scores (data are shown in **Table 1**). Data on treatments and complications were collected up to April 2013. The total number

ORIGINAL ARTICLE

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Dan Med J 2015;62(1):A4999

TABLE 1

Clinical and operation characteristics at the time of the first pump implantation.

Patient no.	Age, yrs+ mo., sex	ITB at end, µg/day	Cause of the CP	CP type[a]	GMFCS	Catheter level	Antibiotics[b]	Pump type, placement
1	12+4, M	485	Asphyxia neonatalis	S	5	th5/6	125 mg cefuroxim	P, SC[c]
2	7+2, M	900	UNK	S	5	th5/6	500 mg cefuroxim	P, SC[c]
3	3+3, M	2,100[d]	Asphyxia neonatalis	SD	5	th6	500 mg cefuroxim	P, SC[e]
4	7+4, F	550	Asphyxia neonatalis	SD	5	th6	25 mg/kg diclocil	P, SC[c]
5	13+2, M	600	Lesch-Nyhan syndrome	SD	5	th7	750 mg cefuroxim	P, SC
6	6+4, M	680[d]	Infection with RSV	S	5	th5	750 mg cefuroxim	P, SC
7	4+3, F	1,100[d]	Congenital malformation of the brain	S	5	th5/6	1.5 g cefuroxim	P, SC
8	5+3, M	1,500[d]	Lesch-Nyhan syndrome	SD	5	th6/7	750 g cefuroxim	P, SC[c]
9	6+6, F	600[d]	Meningitis pneumococcica	SD	5	th5/6	750 mg cefuroxim	P, SC
10	14+1, F	450	Congenital CMV infection	S	5	th5/6	750 mg cefuroxim	P, SC
11	7+5, F	675	UNK	S	5	th5	750 mg cefuroxim	P, SC
12	13+11, M	143	Asphyxia	S	5	th11	750 mg cefuroxim	P, SC
13	13+11, M	760	Perinatal asphyxia	SD	5	th6[f]	750 mg cefuroxim	P, SC[c]
14	14+11, F	750	Congenital CMV infection	S	5	th5/6	1.5 g diclocil	P, SC
15	5+0, F	1,000[d]	Asphyxia neonatalis	S	5	th7	1.5 g Cefuroxim	P, SC
16	4+5, F	200[d]	UNK	S	5	th7	750 mg cefuroxim	P, SC
17	17+10, F	300	Asphyxia	SD	5	th6/7	750 mg cefuroxim	P, SC
18	3+10, M	440[d]	Encephalopathy	SD	5	th7/8	300 mg cefuroxim	P, SC
19	11+10, M	729	Asphyxia neonatalis	S	5	th7	750 mg cefuroxim	P, SC
20	8+11, M	650	Alexander disease	S	5	–	Type not specified	P, UNK
21	13+3, F	144	UNK	D	5	th6/7	750 mg cefuroxim	E, SC
22	15+2, M	120.9	Perinatal asphyxia	S	5	Mid thoracic	1 g diclocil	E, SC
23	3+2, M	235[d]	Graviditas plurifoetatio	S	5	Mid thoracic	1.3 g cefuroxim	E, SC
24	7+2, M	240[d]	*Streptococcus meningitis*	SD	5	Mid thoracic	350 mg cefuroxim	E, SC
25	5+1, M	1,900[d]	Asphyxia neonatalis	S	5	th5[g]	750 mg cefuroxim	P, SC[c]
26	12+1, F	175	Asphyxia neonatalis	S	5	Mid thoracic	750 mg cefuroxim	E, SC[c]
27	14+8, F	356	Asphyxia neonatalis	SD	5	th7	1 g cefuroxim	E, SC[c]
28	5+2, M	650[d]	Asphyxia neonatalis	SD	5	th7	500 mg cefuroxim	E, SC
29	6+8, F	240[d]	Asphyxia neonatalis	S	5	th7	750 mg cefuroxim	P, SC[c]
30	4+7, M	550[d]	Prematurity & infarcts in the brain	S	5	–	0.5 g diclocil	P, SC[c]
31	6+6, F	800	Asphyxia neonatalis	SD	5	–	Diclocil	P, UNK[c]
32	9+2, M	985.68	Asphyxia at birth	S	5	Mid thoracic	UNK	P, SC
33	14+8, M	600[d]	Graviditas plurifoetatio & asphyxia neonatalis	S	5	Low thoracic	750 mg cefuroxim	E, SC
34	5+3, M	135[d]	Bilateral infarct sequelae	S	5	Mid thoracic	750 mg cefuroxim	E, SC
35	7+4, M	250[d]	Graviditas plurifoetatio	SD	5	–	500 mg cefuroxim	E, SC
36	6+9, M	330[d]	Physical abuse	S	5	Mid thoracic	750 mg cefuroxim	E, SC
37	4+8, F	225[d]	Asphyxia neonatalis	S	5	Mid thoracic	375 mg cefuroxim	E, SC
38	6+4, F	300[d]	Praematuritas	S	5	Mid thoracic	750 mg cefuroxim	E, SC
39	5+2, M	550[d]	Asphyxia neonatalis	S	4	Mid thoracic	375 mg cefuroxim	E, SC[c]
40	14+3, F	100[d]	Sclerosis amyotrophica lateralis	S	5	Mid thoracic	750 mg cefuroxim	E, SC
41	5+1, F	150	Asphyxia neonatalis	S	5	th5/6	1.2 g cefuroxim	P, SC
42	11+5, M	550	Dandy-walker syndrome	S	5	th5/6	750 mg cefuroxim	P, SC
43	7+3, M	250	Congenital malformation of the brain	S	5	th5	diclocil 12.5 mg/kg	P, SC
44	15+6, F	343	Congenital CMV infection	S	5	th7	750 mg cefuroxim	P, SC
45	5+1, F	350	Intrauterine infection unspecified	S	5	th7	750 mg cefuroxim	P, SC[c]
46	14+8, M	105.1	Neonatal asphyxia & hypoglycaemia	SD	–	C2	Cefuroxim	E, SC

CMV = cytomegalovirus; CP = cerebral palsy; D = dyskinetic; E = electrical; F = female; GMFCS = Gross Motor Function Classification System; ITB = intrathecal baclofen; M = male; P = pressure-driven; RSV = respiratory syncytialvirus; S = spastic; SC = subcutaneous; SD = spastic/dyskinetic; UNK = unknown.

a) All the spastic patients are tetraplegics.

b) 2nd pump operation: 250 mg diclocil: no. 45; 1 g diclocil: no. 1 & 4; 1.5 g diclicol: no. 25; unk diclocil: no. 26; 500 mg cefuroxim: no. 3, 30 & 39; 750 mg cefuroxim: no. 2, 8, 27 & 29; 1.5 g cefuroxim: no. 13; 37.6 mg/kg cefuroxim: no. 31. 3rd pump operation: 1 g diclocil: no. 3.

c) The patient had a 2nd pump operation where an electrical pump was implanted.

d) Updated June 2014.

e) The patient has had a 2nd and a 3rd pump operation, where a pressure-driven pump and an electrical pump were implanted, respectively.

f) The position of the catheter was changed to th12 at an operation concerning catheter complications.

g) The position of the catheter was changed to th8 at the replacement of the pump.

TABLE 2

Question	Improvement, n					Median score	Yes, n (%)	No, n (%)
	no	subtle	some	good	marked			
1: Change of well-being	5	2	3	8	13	4	–	–
2: Change of function	14	6	4	5	2	2	–	–
3: Ease of care	3	5	7	10	6	3		
4: Treatment worth it	–	–	–	–	–	–	27 (87.1)	4 (12.9)
5: Treatment to be recommended	–	–	–	–	–	–	28 (90.3)	3 (9.7)

Parents' assessment of the efficacy of intrathecal baclofen. Questions 1-3 are worded as follows: To what degree has intrathecal baclofen changed the well-being, functions or ease of care of your child? Questions 4-5: Has intrathecal baclofen been worth it in spite of complications and is the treatment recommendable to other parents?

of years that the children had both pump types, the pressure-driven pump and the electrical pump were 212.0, 164.2 and 47.8 years, respectively. The mean number of pump years per child was 4.6 years (range: 61 days-9.9 years). Adverse events were categorised as mechanical and/or infectious. The Ashworth score of children still associated with the H. C. Andersen Children's Hospital was assessed through June 2014. When the children became adults, they were followed-up by neurologists.

Questionnaire

It was considered relevant to know what effects of ITB the children's parents had noticed. The questionnaire was sent to the parents' addresses; and after around 14 days, the parents were contacted again by phone and invited to participate in an interview. Upon oral consent, an interview was conducted by one of us (TMO). For ethical reasons, parents of children who had died were not contacted. The interview questions are included in **Table 2**.

Statistical analysis

The statistical computer programme STATA 12 was used for the statistical analyses. The non-parametric Wilcoxon matched-pairs signed-rank test was used to compare outcome measures. Results with $p \leq 0.05$ were considered statistically significant. For insight into the effect sizes, means with standard deviations were calculated. The number of days each child had a pump was calculated and incidence rate was calculated as incidents/pump year.

Trial registration: not relevant.

RESULTS

Patients

At their first pump implantation, the children were between 3 years and 3 months and 17 years and 10 months (mean 8.10 years). Twenty were girls and 26 boys. Thirty-one children had spastic CP, 14 had spastic/dyskinetic (mixed type) CP and one had dyskinetic CP. Thirty-three children had epilepsy (71.7%). Eighteen had scoliosis (39.1%).

The cause of CP was prematurity and/or asphyxia and related complications in 21 (45.7%) cases, infection in seven (15.2%), Lesch-Nyhan syndrome in two (4.3%), amyotrophic lateral sclerosis in one (2.2%) and unknown or imprecisely described in 15 (32.6%). A Body Mass Index (BMI) could be calculated for 15 children. Six children were classified as underweight and nine as normal weight. Fourteen children (30.4%) were born pre-term, thirteen (28.3%) at term, and four children (8.7%) were born post-term. For 15 children (32.6%), no gestational age could be precisely determined. GMFCS measures were registered for 45 children (98%). Of those, one child (2.2%) had a score of four and 44 children (97.7%) scored five. All children received physiotherapy and/or occupational therapy with varying intensity and frequency.

Baclofen test before ITB treatment was positive in 39 and negative in one case. Repeated test was not performed, but the pump was still implanted because the parents whished so because it was determined by clinical assessment that the pump would be effective. Testing was attempted in six children, but was unsuccessful due to severe scoliosis.

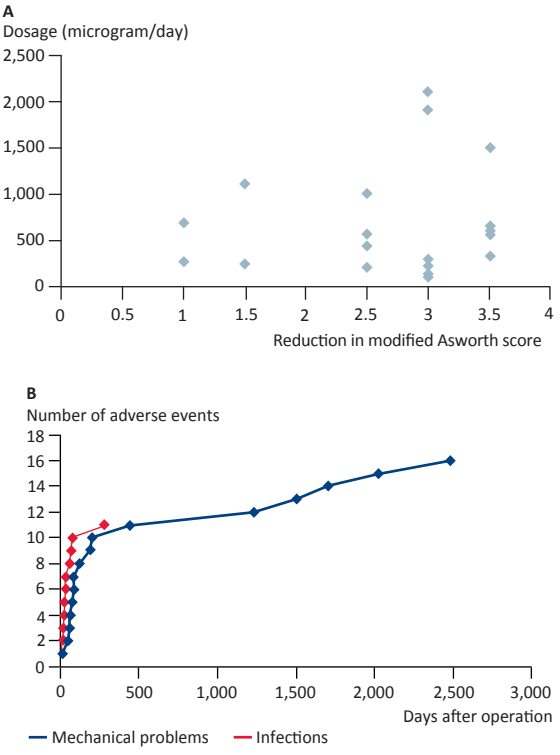
The pump was placed subcutaneously in all 46 patients. The catheter tip was placed between spinal levels Th12 and C2, with 82.6% placed at the mid-thoracic level. The aim is to place the catheter tip at the mid-thoracic level, though it is not always possible to place it as intended due to adherences, among others. All children received intravenous antibiotics preoperatively with doses of cefuroxim ranging from 125 to 750 mg according to weight.

The dosage of ITB was up-regulated in varying dosage steps and intervals, and at the end of the study it was 105.1-2,000 micrograms/day (mean 494.9 micrograms/day).

Eight patients had died. None of the deaths were related to the pump. A total of 35 patients still had the pump at the end of April 2013; all the patients who died had the pump until their deaths or it was removed only a few months before. Three patients did not have the pump at the end of April 2013. Background data are show in Table 1.

FIGURE 1

A. Comparison of current baclofen dosage and reduction in modified Ashworth score. The baclofen dosages administered can vary greatly within the same modified Asworth score reduction. **B.** Number of adverse events over time due to mechanical problems and infections. Infections mostly occurred within two months and that mechanical problems occurred at varying times after implantation.



Modified Ashworth score

By June 2014, the median MAS had been reduced from the initial four to two in the upper extremities and from four to one in the lower extremities.

Anti-spasticity medicine

Oral baclofen was administered to 35 of 46 patients before ITB and was withdrawn in 18 after ITB. Mean oral baclofen was reduced from 27.3 to 17.7 mg/day with a mean difference of 9.7 and a p value of 0.0024. Oral tizanidin was administered in four patients before ITB and was withdrawn in all four after ITB and introduced in another two patients. By June 2014, the ITB doses were registered and correlation between dosages and reduction in MAS are shown in **Figure 1**A, which demonstrates no significant connection.

Questionnaire

As one address could not be obtained and eight children had died, 37 questionnaires were sent out. Of those, 31 parents (83.8%) answered. One parent did not want to participate, and five could not be reached by phone. Questions and data on improvement obtained are shown in Table 2.

Among the 31 parents who answered, 27 (87.1%) experienced that ITP treatment had been beneficial for their child, and 28 parents (90.3%) would recommend ITB treatment to others.

Adverse events

Adverse events were reported in 46 children and are summarized in **Table 3** and Figure 1B demonstrating a temporal relationship.

The total incidence rate was 0.40 per pump year. For device-related complications, the incidence rate was 0.20 per pump year. For the non-device related complications, the incidence rate was 0.14 per pump year. One patient had four incidents with catheter complications and eight patients accounted for ten incidents. In one case, adverse administration of dose was caused by catheter leakage demanding reoperation. This child had a headache of long duration, which resolved after reoperation.

Oedemas and haematomas at the pump site all occurred shortly after operation. On average, infections were identified within two months after pump implantation. All other types of complications occurred at varying times after pump implantation. Adverse event incidence rates were higher with the electrical pump, except for catheter problems, headache and two cases of pump malfunction. Children with mixed-type CP had a higher frequency of adverse events. Exceptions, however, were meningitis, oedema at the pump site and pump malfunctions. The only child with purely dyskinetic CP had no adverse events. Complications are shown in Table 3, and the number of adverse reactions over time in Figure 1B.

DISCUSSION

This study has summarised our experience with ITB in 46 paediatric patients from the Region of Southern Denmark covering an average treatment period of 4.6 years per person. The results showed a reduction in spasticity from a median MAS of four to two after ITB. This is parallel to other studies reporting a significant reduction in spasticity with ITB [3-7]. The reduction in oral anti-spasticity medicine was not significant for tizanidin, but it was significant for baclofen as a reduction of a mean daily dosage from 27.3 to 17.7 mg/day after ITB ($p < 0.01$) was observed. Among the patients on oral baclofen before ITB, 51.4% (18/35) received no oral baclofen at the end of the study period. In parallel studies, oral anti-spasticity medication was reduced by 50% and 70% [10, 11].

Parents were satisfied with the ITB treatment. They reported a change in well-being, a change in function

TABLE 3

Complications[a] to intrathecal baclofen therapy.

	Incidents, n	Patients, n	Incidents/ pump year	Incidence rate, Pressure-driven vs electrical pump	Spastic vs spastic/ dyskinetic CP, %[b]	Post-operative days, mean	Re-operations, n
Operation complications							
Per operation	0	0	NA	NA	NA	NA	NA
Oedema	10	9	0.047	0.037 vs. 0.084	22.6 vs. 21.4	8.4	0
Haematoma	5	5	0.024	0.006 vs. 0.084	6.5 vs. 21.4	5.2	3
Infection at the pump or back	8	5	0.038	0.012 vs. 0.126	3.2 vs. 14.3	57.3	7[c, d]
Meningitis	3	3	0.014	0.006 vs. 0.042	19.4 vs. 14.3		
CSF leakage	15	10	0.071	0.055 vs. 0.126	25.8 vs. 50	319.8	11
Headache	1	1	0.005	0.006 vs. 0	0 vs. 7.1	85	1
Catheter complications[e]	14	9	0.066	0.067 vs. 0.063	29.0 vs. 35.7	472.3	14
Malfunction of the pump	2	2	0.009	0.012 vs. 0	6.5 vs. 0	1,856.5	2[c]
Side effects of baclofen[f]	15	13	0.071	0.049 vs. 0.146	25.8 vs. 50	398.9	1
Administration errors	9	9	0.042	0.018 vs. 0.126	9.7 vs. 42.9	533.4	0
Complications caused by other surgeries	2	2	0.009	NA	NA	NA	NA

CP = cerebral palsy; CSF = cerebrospinal fluid; NA = not applicable.
a) Non-device-related complications: headache, side effects of baclofen, administration errors and haematoma.
Device-related complications: infection, CSF leakage, catheter complications, and malfunction of the pump.
b) Percentage of the total number with spastic cerebral palsy or spastic/dyskinetic cerebral palsy.
c) The pump was removed.
d) 1 of the reoperations only led to removal of the catheter.
e) 5 lesions, 2 kinks, 1 no passage, 2 breaks, 3 disconnections, 1 dislocation.
f) 9 overdosages, 3 withdrawal/abstinence symptoms, 3 underdosages.

and a change in ease of care of their child of median 4 (good improvement), 2 (subtle improvement) and 3 (some improvement), respectively. One study demonstrated that caregivers had seen a positive change in well-being, function and ease of care with ITB treatment [11]. In this study, most parents (87.1%) answered that they thought it had been worthwhile to get the ITB treatment, and 90.3% would recommend this treatment to other parents. This is in line with what has been found in other studies, where 91.7% and 81% thought that it had been worthwhile, and 91.7% and 87% would recommend ITB therapy [11, 12]. Of the ones who would not recommend ITB, two had more than one adverse event and one did not experience as much efficacy.

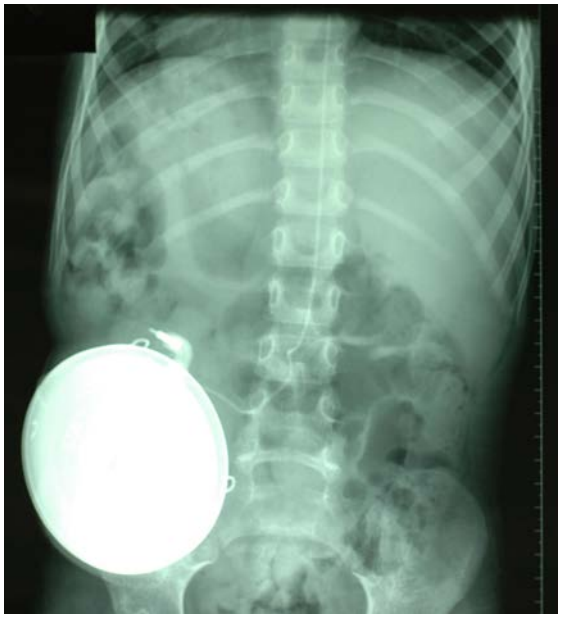
The children in this study received an ITB dosage of 105.1-2000 µg/day (mean 494.9 µg/day). This is similar to what has been reported in other studies with a treatment duration of several years, where the mean dosage was between 350-576 µg/day [10, 11, 13], but the reported mean dosages were much higher than dosages reported in studies where treatment periods were closer to 1-1.5 years; in these studies the mean dosage was 157-233 µg/day [5, 7, 14].

Most often adverse events known to occur have been cerebrospinal fluid (CSF) leak, infection and catheter problems. Even though the complications may be similar in nature and frequency to those reported in other studies, it is difficult to make a direct comparison with such other studies as there is no standardised method of reporting such complications. In the present study, the total complication rate was 0.40 incidents per pump year.

The incidence rates for device-related complications and non-device-related complications were 0.20 and 0.14 per pump year, respectively. These figures are close to those reported in another study which found a total complication rate of 0.38 per year [6]. The types of complications included were similar to those found in our study. However, the number of reported complications is lower than in other studies reporting a device-related complication rate of 0.48 and 1.08 per year and a non-device related complication rate of 2.1 and 1.92 per year [10, 14].

This difference could arise because different events were included in the calculation of device-related and non-device-related complications. For example, events like back pain at pump site level, transaction of catheter during orthopaedic surgery and lack of efficacy were included in the term device-related events in these other studies. Furthermore, bedsores, drooling and constipation were covered by the concept non-device-related complications [10, 14].

We found that complications occurred more often in children with mixed-type CP than in children with spastic CP. This has also been concluded in another study [6]. The incidence rates for the electrical pump



X-ray of a child with a baclofen pump and connecting intrathecal catheter.

were higher than for the pressure-driven pump for all types of incidents except for catheter problems, headache and the two pump malfunctions. This may be so because more treatment years were calculated for pressure-driven pumps than for electrical pumps. It could also be related to the fact that administration errors leading to adverse events may be more common when handling electrical pumps than when handling pressure-driven pumps. Administration errors were followed by new instructions for refill procedures (electronic pump).

Pump explantation was required in 13.1 (8/61) of the ITB pumps we implanted. This figure is both lower and higher than the 44% and 4.8% reported in two other studies [3, 5], where 75% and 25% of the pump explantations happened due to infection at the pump site and due to pump malfunctions, respectively. In our study, infections were identified on average within 2 months after pump implantation. This indicates that most infections occurred in relation to pump implantation and not in association with pump fillings, even though regular needle penetration through skin could be a source of contamination in pump pockets.

CONCLUSION

This study demonstrated that ITB resulted in reduced spasticity in children with spastic and mixed-type CP, that this reduction was considered beneficial to the children, and that treatment can be considered safe. Most common complications were infections, CSF leak and catheter problems with a total complication rate of 0.40 per pump year. Hence, on average, each child with ITB could live for 2.5 years without any adverse event. Parent satisfaction with ITB was high and ITB was recommendable.

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ACCEPTED: 24 November 2014

CONFLICTS OF INTEREST: none. Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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