Survival of individuals with cerebral palsy receiving continuous intrathecal baclofen treatment: a matched-cohort study

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LIST OF ABBREVIATIONS

CDER	Client Development Evaluation Report
DDS	California Department of Developmental Services
ITB	Intrathecal baclofen

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AIM To determine whether intrathecal baclofen (ITB) changes mortality risk in persons with cerebral palsy (CP).
METHOD Records were reviewed for all persons with CP who were managed with ITB for hypertonicity at a specialty hospital in Minnesota between May 1993 and August 2007. A comparison cohort was randomly selected from clients of the California Department of Developmental Services who were initially evaluated between 1987 and 1990 and were matched to those with ITB for age, sex, Gross Motor Function Classification System (GMFCS) level, presence or absence of epilepsy, and feeding-tube use. Survival probabilities were estimated using the Kaplan–Meier method, and differences were tested via log-rank.
RESULTS Three hundred and fifty-nine persons with CP (202 males, 157 females) receiving ITB for hypertonicity (mean age 12y 8mo, SD 7y 9mo, range 3y 1mo to 39y 9mo) were matched to 349 persons without ITB pumps (195 males, 154 females; mean age 12y 7mo, SD 8y 4mo, range 2y 7mo to 40y). The proportion of patients at different GMFCS levels in the ITB and in the non-ITB cohorts, respectively, was as follows: level II 3% and 3%, level III 16% and 16%, level IV 38% and 37%, and level V 43% and 44%. Survival at 8 years of follow-up was 92% (SD 1.9%) in the ITB cohort and 82% (SD 2.4%) in the non-ITB cohort ($p<0.001$). After adjustment to account for recent trends in improved survival in CP, 8-year survival in the non-ITB cohort was 88%, which was not significantly different from the ITB cohort ($p=0.073$).
INTERPRETATION ITB therapy does not increase mortality in individuals with CP and may suggest an increase in life expectancy.

Cerebral palsy (CP) is the most common congenital cause of disability in children, affecting approximately 2 to 3 per 1000 live births.[1] Spasticity is reported in approximately 70% of those with CP and is thought to interfere with function and comfort. Baclofen is a derivative of gamma-aminobutyric acid that is used to treat spasticity. The effectiveness of oral baclofen is limited by its sedating side effects, so the drug is often administered intrathecally by continuous infusion to deliver it to the site of action, the spinal cord. Intrathecal baclofen (ITB), which was approved by the US Food and Drug Administration in 1996 for use in individuals with CP, is effective in the reduction of spasticity as well as dystonia and is frequently used to treat hypertonicity associated with CP.[2–4] In addition to the long-term reduction of hypertonicity, authors have reported improvement in comfort, positioning, ease of care provision, and motor function in select groups of individuals, and a reduction in the anticipated need for orthopedic surgery.[2,5,6] Progression of hip dislocation may be reduced with ITB, although the effect of ITB on the progression of scoliosis is controversial.[7–10]

ITB therapy involves the surgical implantation of a programmable pump with a reservoir for the continuous delivery of baclofen to the intrathecal space. As such, it is associated with risks related to surgery, hardware, and the drug itself: for example, the presence of a foreign body

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results in a risk of infection, hardware can malfunction, acute withdrawal of ITB can result in a potentially life-threatening syndrome, and significant overdose of ITB can result in respiratory depression.[11,12]

ITB is most frequently used in individuals with severe motor impairment who are at the greatest risk of reduced life expectancy compared with their typically developing peers. Numerous studies have identified factors associated with mortality and survival of persons with CP. Mortality rates are higher, and survival probabilities lower, for those with more severe CP, severity being measured by simple functional variables including gross and fine motor skills (ambulation, rolling, or crawling) and feeding ability.[12–16] Comparisons of survival rates in persons with CP in the USA, the UK, and Australia that have accounted for these basic functional variables reveal remarkably similar results.[17] Epilepsy and degree of mental retardation* can further adversely affect survival.[16,18] The purpose of the present study was to determine whether ongoing management of hypertonia with ITB is associated with an increase in the long-term risk of mortality in persons with CP.

METHOD

After University of Minnesota Institutional Review Board approval, medical records were reviewed and abstracted for a consecutive series of persons followed at Gillette Children's Specialty Healthcare in St Paul, MN, USA, who were receiving ITB for management of increased muscle tone due to static encephalopathy, and who had their pumps placed between May 1993 and August 2007. Those with acquired brain injury, neurodegenerative disorders, or spinal-cord injury were excluded, as was one person who was 57 years old at the time of pump placement and thus more than 2SD above the average age and more than 17 years older than the next oldest person. The overall size of the cohort was determined by the number of individuals who were receiving ITB management at the hospital on a regular basis, excluding those who had their implant surgery at the hospital but planned all pump management at a location closer to their homes. The hospital serves a wide geographic area, including the US states of Minnesota, North Dakota, South Dakota, Iowa, and portions of Wisconsin and Nebraska.

A control cohort with CP but not receiving ITB treatment and excluding those with brain damage of postnatal origin, such as traumatic brain injury or near drowning, degenerative disorders, or genetic anomalies, was randomly selected from clients of the California Department of Developmental Services (DDS) who used the services at least once between January 1987 and December 1990. This period was selected to ensure that the control cohort was not receiving ITB therapy (as it was before the approval of ITB for use in CP) and to allow sufficient follow-up time to estimate survival to approximately 8 years. Services provided by the DDS include medical treatment, occupational or physical therapy, case management, and social services. Individuals receiving services from the DDS are evaluated approximately once a year with a structured interview known as the Client Development Evaluation Report (CDER);[19] this instrument contains over 200 psychological, medical, functional, behavioral, and cognitive items, and the reliability of the functional items has been assessed and judged to be satisfactory.[20]

From the medical records of the Minnesota ITB and California non-ITB cohorts, we extracted information on each person's age, sex, presence or absence of epilepsy, use of feeding tubes, presence of spasticity or dystonia, and functional status. In the Minnesota ITB cohort, functional status was determined by one of the authors (LEK), who determined the Gross Motor Function Classification System (GMFCS)[21] level at the time-point closest to the date of pump implantation when the patient had sufficient information recorded in the medical chart. In the California non-ITB cohort, functional status was measured using the CDER and converted to a GMFCS level using the CDER variables of rolling and sitting, crawling and standing, walking, and stair climbing.

Each person in the Minnesota ITB cohort was placed into one of 240 bins according to the following criteria measured at time of pump placement: age (in 5-year groupings: 2y 6mo to <7y 6mo, 7y 6mo to <12y 6mo, 12y 6mo to <17y 6mo, 17y 6mo to <22y 6mo, and 22y 6mo to <27y 6mo, with a final group of 27y 6mo to <40y), sex, presence or absence of epilepsy, feeding-tube use, and GMFCS level (I–V).

Persons from the California non-ITB cohort were also placed into one of the 240 bins described above, with the criteria measured at the earliest DDS evaluation between 1987 and 1990, so that the numbers in each bin were similar to those for the Minnesota ITB cohort. In a few cases, insufficient numbers were available in the California non-ITB cohort, so the final number is 10 fewer than in the Minnesota ITB cohort. A complete description of the selection of the California non-ITB cohort and matching technique is provided in Figure 1.

In the Minnesota ITB cohort, most individuals were followed periodically. If they were not receiving their routine pump care at Gillette, a simple survey inquiring about the status of the individuals and their ITB pump was sent to the last known address after institutional

*UK usage: learning disability.

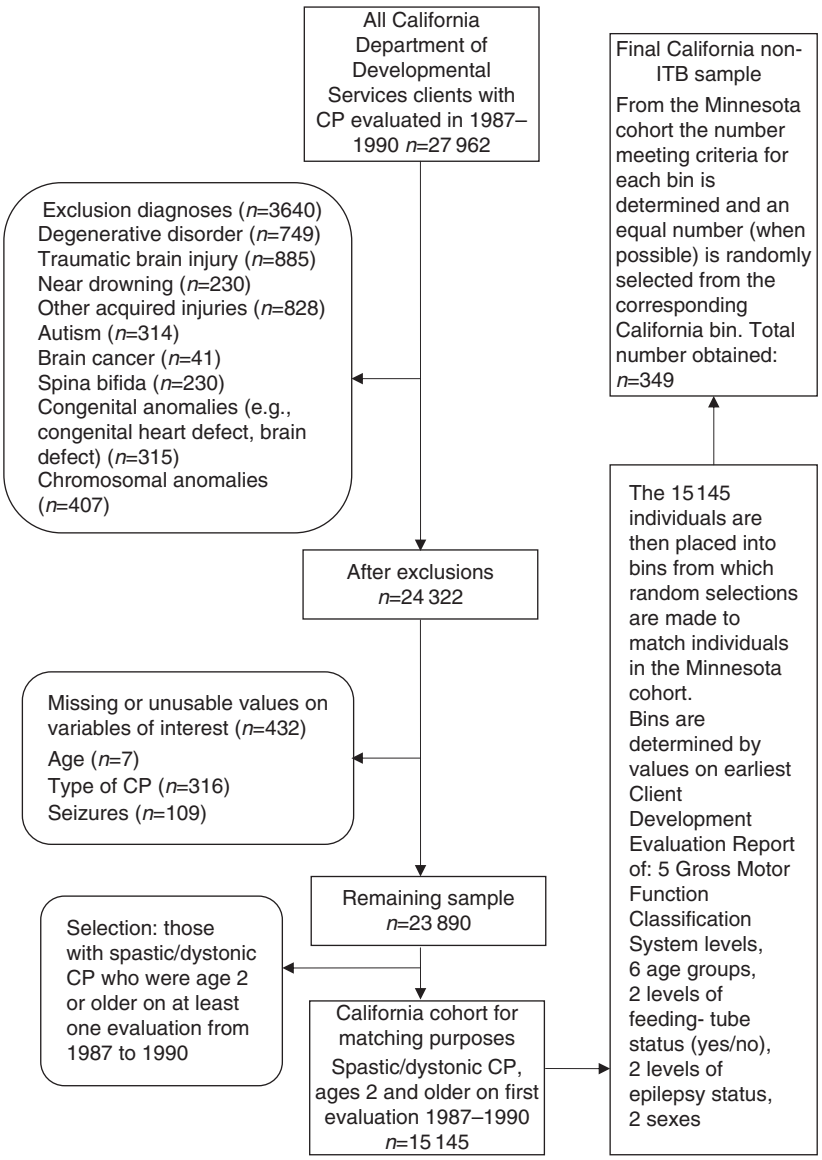

Figure 1: Selection of the California cohort of persons with cerebral palsy (CP) without intrathecal baclofen (ITB) pumps.

review board approval for that contact. If letters to patients or their families were returned without a forwarding address, the last known pump-managing provider was contacted for information. If contact could not be established, the Minnesota Death Certificate Index (http://people.mnhs.org/dci/search.cfm) and North Dakota Department of Public Health Public Death Index (https://secure.apps.state.nd.us/doh/certificates/deathCertSearch.htm) were searched to ascertain whether a date of death could be found for those individuals. For the California non-ITB cohort, we obtained mortality information from electronic files from the California Department of Health Services.[22]

Statistical analysis

Survival probabilities were estimated for each cohort using the Kaplan–Meier method, and differences were tested by the log-rank test.[23] Time zero was the date of implantation of the ITB pump for the Minnesota cohort or earliest DDS evaluation between 1987 and 1990 for the California non-ITB cohort. Those in the ITB cohort who were continuing follow-up at Gillette were censored on 31 December 2007. Persons in the Minnesota ITB cohort without recent follow-up who did not respond to the mailed survey were censored at 1.5 months after last contact. Of the 359 persons in the Minnesota ITB cohort, 12 (3%) were lost to follow-up and were therefore censored 1.5 months after their last

contact. For those in the California non-ITB cohort, the corresponding rule was to censor 6 months after last DDS evaluation or on 31 December 1995, whichever was earlier. This rule applied to approximately 15% of the entire California non-ITB cohort (and to a similar proportion of the final random sample).

To estimate how much of the difference in survival probabilities may have been due to overall improvement in survival from the earlier period of the California non-ITB cohort follow-up to the later period of the Minnesota ITB cohort follow-up, an adjustment was made based on a decline in mortality rate of 3.4% per year reported by Strauss et al.[15] for children with severe CP (roughly equivalent to GMFCS levels IV and V) and children and adults fed by feeding tube.

Statistical analyses were carried out using SAS/STAT version 6.12 (SAS Institute, Cary, NC, USA), with S-PLUS version 4.0 (Insightful Corp./Tibco Spotfire, Palo Alto, CA, USA) used for graphics.

RESULTS

After exclusions, 359 participants with ITB pumps from Gillette (Minnesota) were identified (202 males, 157 females; mean age 12y 8mo, SD 7y 9mo, range 3y 1mo to 39y 9mo). The number in the comparison cohort from California without ITB pumps matching these was 349 (195 males, 154 females; mean age 12y 7mo, SD 8y 4mo, range 2y 7mo to 40y). The distribution of participants by GMFCS level, gastrostomy versus oral feeding, presence or absence of epilepsy, and age is shown in Table I.

The mean follow-up was 6 years 2 months (SD 3y) in the Minnesota ITB cohort and 6 years 2 months (SD 2y 6mo) in the California non-ITB cohort. During follow-up there were 21 deaths in the Minnesota ITB cohort and 50 deaths in the California non-ITB cohort. Survival at 8 years after time zero was 92% (SD 1.9%) in the Minnesota ITB cohort and 82% (SD 2.4%) in the California non-ITB cohort (Fig. 2). These were statistically significantly different ($p<0.001$). However, the cohorts were not matched for calendar year; with an approximate adjustment to account for recent trends in improved survival in CP as reported by Strauss et al.,[15] the 8-year survival in the California non-ITB cohort increases to 88% (Fig. 3). Assuming the adjustment to be exact and using adjusted observed and expected numbers of deaths in the California non-ITB cohort in calculating the log-rank statistic, the difference in survival curves was no longer significant ($p=0.073$).

Table I: Demographics of persons with cerebral palsy with (Minnesota) and without (California) intrathecal baclofen (ITB) pumps

	Minnesota ITB	California non-ITB
Persons, *n*	359	349
First observed, year[a]	1993–2007 (mean 2000)	1987–1990 (mean 1988)
GMFCS level, *n* (%)		
II	12 (3)	12 (3)
III	56 (16)	56 (16)
IV	135 (38)	129 (37)
V	156 (43)	152 (44)
Feeding tube, *n* (%)		
Yes	120 (34)	111 (32)
No	238 (66)	238 (68)
Epilepsy, *n* (%)		
Yes	148 (41)	147 (42)
No	210 (58)	202 (58)
Sex, *n* (%)		
Male	202 (56)	195 (56)
Female	157 (44)	154 (44)
Age, *n* (%)		
2y 6mo to <7y 6mo	97 (27)	97 (28)
7y 6mo to <12y 6mo	122 (35)	131 (36)
12y 6mo to <17y 6mo	53 (15)	53 (15)
17y 6mo to <22y 6mo	38 (11)	38 (11)
22y 6mo to <27y 6mo	14 (4)	13 (4)
27y 6mo to <40y	26 (7)	26 (7)

[a]Year pump placed in the Minnesota ITB cohort. GMFCS, Gross Motor Function Classification System.

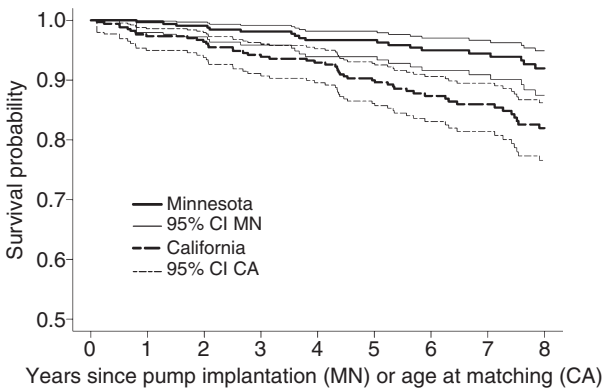

Figure 2: Survival of persons with cerebral palsy with (Minnesota, MN) and without (California, CA) intrathecal baclofen pumps. CI, confidence interval.

DISCUSSION

ITB pumps are usually implanted in persons with CP who are most at risk for premature death, so we were concerned that the risks known to be associated with ITB might further adversely affect survival. We are reassured that our study has shown that survival is comparable to, or somewhat better than, a matched cohort without pumps. The

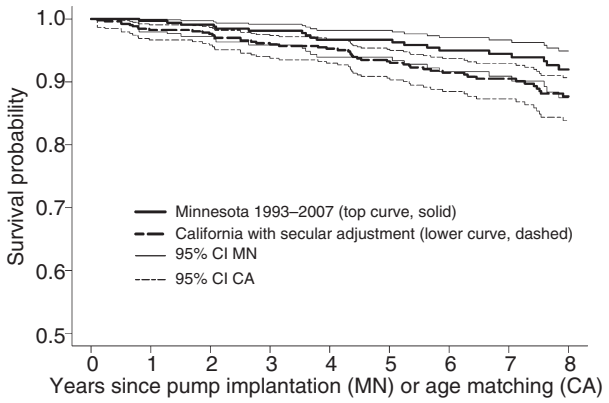

Figure 3: Survival of persons with cerebral palsy with (Minnesota, MN) and without (California, CA) intrathecal baclofen pumps, with secular adjustment. CI, confidence interval.

survival in California has been shown to agree closely with that in the UK and Australia (matched for important functional variables).[17] The only outcome addressed in our study is survival; other benefits of ITB therapy have been previously reported and include tone reduction, comfort, ease of care, and decrease in number of anticipated orthopedic procedures.[3,5,24–27]

The most obvious limitation of the present study was that the cohorts were not prospectively randomly assigned. However, blinding of observation would not be relevant with the outcome measure of survival, and implementation of a randomly assigned study would be impossible in current practice. In addition to the lack of random assignment to treatment groups that could have lead to selection bias, our comparison was further compromised by the fact that the cohorts were not contemporaneous, and secular trend adjustments can only be approximate. The adjustment made to account for the decline in mortality rates from 1988 to 2000 was based on results for children aged up to 15 years with the most severe impairments due to CP and for children and adults who were fed by gastrostomy tube.[15] As approximately 36% of the California non-ITB cohort in the present study were functioning at higher levels or were older and not fed via gastrostomy, the adjustment (from Figs 2 and 3) may overestimate the improvement in survival in the California non-ITB cohort. In any event, it is unclear how much of the improved survival over recent years might be attributable to improvements and innovations in medical care and treatment, which may include ITB therapy.

Another limitation relates to the assignment of GMFCS level, and thus the matching of the cohorts by level of motor function. Assignment of GMFCS levels was methodologically different for the two cohorts, and conversion of motor function information on the California CDER to GMFCS level has not been validated. Assuming that the matching of GMFCS levels is appropriate, there is a further limitation relative to the survival analyses, as, within a given level of GMFCS, differences in level of gross motor function may still exist and can affect survival.

Finally, the analyses were retrospective and involved cohorts followed by different professionals at different locations, and with different frequencies of follow-up. For persons who were lost to follow-up, data were censored 1.5 months after last contact in the Minnesota ITB cohort and 6 months after last DDS evaluation in the California non-ITB cohort. These censoring rules were used (rather than censoring exactly at time after the last visit or evaluation), as visits typically occurred every 3 to 6 months in Gillette (Minnesota), and annually in California. However, variations in the censoring rule, including censoring at time of last contact, had only a marginal impact on the actual estimates of survival. For example, censoring exactly at the time of last contact changed the estimated 8-year probability of survival from 92.0% to 91.9% for the Minnesota ITB cohort and from 82.0% to 81.8% for the California non-ITB cohort.

Notwithstanding the stated limitations, clinicians can find some reassurance in the finding that survival in persons with CP who have severe motor impairment appears not to be adversely affected, and could possibly be improved, with ITB therapy. It will be challenging to design and implement a study to address this question more definitively.

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