Efficacy of Human Botulism Immune Globulin for the Treatment of Infant Botulism: The First 12 Years Post Licensure

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Objectives To report the efficacy of Human Botulism Immune Globulin Intravenous (BIG-IV) in the first 12 years following its licensure in 2003 and to characterize its use nationwide in treating patients with infant botulism.

Study design Medical records and billing information were collected for US patients treated with BIG-IV from 2003 to 2015. Length of hospital stay (LOS) and hospital charge information for treated patients were compared with the BIG-IV Pivotal Clinical Trial Placebo Group to quantify decreases in LOS and hospital charges.

Results The use of BIG-IV reduced mean LOS from 5.7 to 2.2 weeks. This shortened hospital stay resulted in a mean decrease in hospital charges of $88 900 per patient. For all US patients 2003-2015, total decreases in LOS and hospital charges were 66.9 years and $86.2 million, respectively. The decrease in mean LOS was time dependent: BIG-IV treatment on hospital days 0-3 reduced mean LOS by 3.7 weeks ($P < .001$ vs the BIG-IV Pivotal Clinical Trial Placebo Group), on hospital days 4-7 by 2.6 weeks ($P < .001$ vs the BIG-IV Pivotal Clinical Trial Placebo Group) and on hospital days 8-10 by just 1 week (P = NS). Since licensure, 1192 patients in 48 states and Washington, DC, have been treated with BIG-IV.

Conclusions The use of BIG-IV since its licensure in 2003 treated approximately 93% of US patients with laboratory-confirmed infant botulism, and prevented >65 years in hospital stay and >$85 million in hospital charges from occurring. The greatest LOS reduction was achieved when BIG-IV was administered soon after hospital admission. Effective and appropriate use of BIG-IV in the US has continued in the postlicensure period. *(J Pediatr 2017;■■:■■-■■).*

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Infant botulism is an acute, life-threatening paralytic infectious disease of infants and is the most common form of human botulism in the US.[1] Infant botulism results when swallowed spores of *Clostridium botulinum* (or rarely, neurotoxigenic *Clostridium baratii* or *Clostridium butyricum*) germinate and produce botulinum neurotoxin in the infant's large intestine. The absorbed toxin is transported by the circulation to the neuromuscular junction, where it blocks release of acetylcholine and causes flaccid paralysis.[2] Botulinum neurotoxin exists in 8 antigenic variants (A-H) that are distinguished by the inability of a polyclonal antitoxin raised against 1 toxin type to neutralize any of the other 7 toxin types in the standard mouse bioassay.[3,4]

Before the development of Human Botulism Immune Globulin Intravenous (BIG-IV), the treatment of patients with infant botulism consisted only of meticulous nutritional and respiratory supportive care.[5] Severely paralyzed patients often were hospitalized for several months before recovering sufficient strength to enable discharge.[6] Before BIG-IV became available, equine-derived immunoglobulin G botulinum antitoxins were not used to treat patients with infant botulism in the US because of safety concerns and their short in vivo half-lives.[7] In 1990-1992, the California Department of Public Health (CDPH) made BIG-IV from hyperimmune plasma donated by volunteers who had been boosted with an investigational (ie, unlicensed) botulinum toxoid. In 1992-1997, the CDPH conducted a phase III pivotal clinical trial of BIG-IV that demonstrated safety and efficacy by reducing the mean hospital stay by 3.1 weeks and mean hospital charges by $88 600 in 2004 US dollars ($112 300 when adjusted into 2015 US dollars).[8] After 6 years of nationwide open-label distribution as an investigational new drug that treated a life-threatening illness and filled an unmet medical need, BIG-IV was licensed by the US Food and Drug Administration (FDA) to CDPH on October 23, 2003, under its proprietary name BabyBIG.[5,8] BIG-IV is a public service (ie, not-for-profit) orphan drug that CDPH provides nationwide in accord with the

BIG-IV	Human Botulism Immune Globulin Intravenous
CDPH	California Department of Public Health
FDA	US Food and Drug Administration
HD	Hospital day, that is, numerical day of hospitalization
LOS	Length of hospital stay
PCTPG	BIG-IV Pivotal Clinical Trial Placebo Group

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Supported by the Infant Botulism Treatment and Prevention Fund of the California Department of Public Health. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.10.035

federal Orphan Drug Act and state law. BIG-IV is the first and only treatment for infant botulism licensed in the US and, as such, constitutes first-line therapy for infant botulism.

As the US license-holder for BIG-IV, CDPH has continued to monitor its efficacy following licensure as measured by decreases in length of hospital stay (LOS) and in hospital charges.[9] Here we report the use and continued efficacy of BIG-IV throughout the US in its 12 years since licensure. We also report the benefit to efficacy of prompt treatment.

Methods

CDPH produces and distributes this human-derived medicine nationwide as required by the federal Orphan Drug Act and state law. As the sole source of BIG-IV in the world, CDPH knew of all US patients treated with BIG-IV for suspected or laboratory-confirmed infant botulism in the 12 years that followed its licensure in 2003. Demographic information was obtained from medical records at the time of treatment. Information on laboratory-confirmed patients with infant botulism in the US not treated with BIG-IV was gathered from annual Council of State and Territorial Epidemiologists National Botulism Surveillance summaries.[1] All infants treated with BIG-IV had an enema or fecal specimen tested for the presence of botulinum neurotoxin and/or *C botulinum* at an approved laboratory using standard methods to establish the diagnosis of infant botulism and determine toxin type.[3]

This study included all laboratory-confirmed patients with infant botulism in the US with illness caused by botulinum toxin type A or type B, which together accounted for >99% of all infant cases of botulism in the US in the study period. Patients with dual toxin type Ba and type Bf accounted for approximately 1% of the study population and were assigned to the toxin type B illness category.

LOS was defined as the total number of full days the patient was hospitalized. As authorized by federal regulations,[9] to determine admission and discharge dates, discharge summaries were obtained for all hospitalizations related to the patient's illness with infant botulism. For each patient's inpatient stay, itemized hospital bills also were obtained to determine the total charges billed for the hospital stay.[9] Hospital charges were used as a surrogate for the cost of the illness. These charges do not include the fees of the attending physicians, unless these were billed through the hospital, the costs of transferring the patient by ambulance, or indirect costs to parents such as lost work time and hotel bills. The marked-up statutorily-required fee ($45 300) for BIG-IV charged by the hospital to the patient was subtracted from the hospital charges before analysis because this amount varied by several orders of magnitude among hospitals. Using information from the US Bureau of Labor Statistics (https://www.bls.gov/data/) for the San Francisco metropolitan area, the Los Angeles metropolitan area, the New York–New Jersey metropolitan area, and the Philadelphia–New Jersey metropolitan area, all hospital charges were adjusted annually into current-year dollars using the lowest percentage increase in medical costs in the previous year that occurred in 1 of these 4 metropolitan regions. Adjusted hospital charges are reported in 2015 US dollars.

Mean LOS and hospital charges were compared with the 1992-1997 BIG-IV Pivotal Clinical Trial Placebo Group (PCTPG)[8] to quantify reductions in these outcome measures. Total reductions in LOS and hospital charges were calculated for type A and type B illness separately and then summed to obtain the cumulative total.

Hospital day (HD) of treatment was defined as the difference between the date of treatment and the date of hospital admission for the continuous hospitalization during which BIG-IV was given. Before licensure, open-label distribution of BIG-IV demonstrated efficacy only when administered within the first 7 days of hospitalization.[8] For this reason, only infants in the US treated with BIG-IV within the first 7 days of hospital admission were included in the mean and cumulative efficacy calculations. All patients treated with BIG-IV in the US in the study period, regardless of HD of treatment, were included in the calculation of mean LOS and hospital charges by treatment day category.

Statistical Analyses

The 2-sample *t* test was used to compare outcomes (eg, LOS or hospital charges) across treatment and placebo groups. In all such comparisons, the reported *P* values used the more conservative value for tests that (i) assumed equal variances, or (ii) assumed unequal variances. In addition, Kolmogorov-Smirnov exact *P* values were also calculated. The Kolmogorov-Smirnov test examines the similarity of the entire distributions of reported outcomes, whereas the *t* test examines a shift in the mean only. Test of trend was also performed for efficacy variables across all treatment day categories.

Results

In the 12 years that followed FDA licensure of BIG-IV in October 2003, the medicine was administered to 1192 patients with infant botulism in the US. Of these patients, 1133 (95%) received BIG-IV within the first 7 days of hospitalization (**Tables I** and **II**). The mean LOS of these patients was 2.2 weeks ($P = .0001$ vs PCTPG) and their mean hospital charges were $118 600 ($P = .001$ vs PCTPG). The cumulative LOS avoided and cumulative hospital charges avoided by use of BIG-IV for all patients treated within 7 days of hospital admission 2003-2015 were calculated to be 66.9 years and $86 201 700, respectively (**Table I**).

Mean LOS and hospitalization charges differed between patients with illness caused by toxin type A and illness caused by toxin type B (**Table II**). Patients with illness caused by toxin type A had a mean LOS of 2.4 weeks and mean hospital charges of $135 600, and patients with illness caused by toxin type B had a mean LOS of 2.0 weeks and mean hospital charges of $107 000. Compared with PCTPG, type A patients had larger mean LOS reductions (4.3 weeks) and hospital charges savings ($96 400) than the type B patients did (2.2 weeks and $63 400, respectively). Cumulative LOS reductions and hospital charges

FLA 5.5.0 DTD ■ YMPD9543_proof ■ December 8, 2017