Russian consensus on the use of incobotulinumtoxinA in children with cerebral palsy for the treatment of spasticity and sialorrhea

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Botulinum therapy for cerebral palsy (CP) is considered not only as one of the effective approaches for the treatment of increased muscle tone and spasticity, but also as a method of excessive salivation correction. The article presents an overview of the results of Russian and foreign studies on the efficacy and safety of incobotulinumtoxinA for the treatment of spasticity of the lower and upper limbs, as well as sialorrhea in patients with CP. The article also provides a consensus opinion of Russian specialists working with patients with CP and using Xeomin (incobotulinumtoxinA) in their practice for the treatment of spasticity and sialorrhea. This consensus was based on the results of a Russian retrospective multicenter study on the use of incobotulinumtoxinA for the treatment of spasticity and sialorrhea in CP, data from recently published international clinical trials, and our own clinical experience. We present detailed practical recommendations on the calculation of the total dose of incobotulinumtoxinA per procedure for the treatment of spasticity in CP, on the calculation of incobotulinumtoxinA dose for the most common target muscles (lower and upper limbs) for spasticity treatment in CP, on incobotulinumtoxinA dilution and dose calculation for sialorrhea treatment in children, on incobotulinumtoxinA dilution and dose calculation for simultaneous treatment of spasticity and sialorrhea in CP. We justify incobotulinumtoxinA use, when simultaneous treatment of spasticity and sialorrhea is necessary, which allows reducing the intervals between repeated injection cycles. IncobotulinumtoxinA use in children with CP demonstrates a favorable safety profile, including long-term use.

Keywords: *cerebral palsy; botulinum therapy; incobotulinumtoxinA; lower limbs spasticity; upper limbs spasticity; sialorrhea; total dose.*
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Background of cerebral palsy treatment

The management of patients with cerebral palsy (CP) is a complex medical and social problem, which is associated with a large number of patients, the development of severe disability in a large percentage of cases, and significant restrictions in socialization [1]. The development of CP in children leads to a whole range of problems in the family and its environment. Therefore, the current standard of treatment of CP also implies a whole range of measures aimed at maximum compensation of existing disorders and optimal integration of the patient into society [2].

Therapeutic approaches using the botulinum therapy method

Botulinum therapy for CP is currently considered as one of the effective approaches for the treatment of hypertonia and spasticity [3, 4], improvement of motor abilities [5–7], posture optimization [8, 9], prevention of secondary orthopedic complications [10–12], correction for strabismus [13], and reduction of sialorrhea [14, 15].

The use of botulinum toxin type A (BTA) products for CP is reflected in international and European consensuses and established in many national guidelines [3, 16, 17].

Currently, there is a significant number of BTA products approved for use in Russia, four of them (Botox, Dysport, Xeomin and Relatox) are recommended for use in children with spastic CP. Only Xeomin (incobotulinumtoxinA) has official indications for the treatment of spasticity and chronic sialorrhea in the Instruction for Medical Use and is approved for CP patients aged 2 to 18 years[1].

Efficacy and safety of IncobotulinumtoxinA for the treatment of spasticity of the lower and upper limbs in patients with CP

IncobotulinumtoxinA was authorized in Russia in 2017 based on the results of a multicenter, open-label, comparative, randomized study to assess the clinical and neurophysiological efficacy of Xeomin vs. Botox in children with spastic equinus and equinovarus foot deformity in CP [18]. This study showed that treatment with Xeomin under the proposed study protocol had proved high clinical efficacy by a significant, persistent, long-term reduction of gastrocnemius muscle spasticity and an increase in the range of motion in the ankle joints during passive and voluntary foot extension. Moreover, a significant number of patients (45.1 %) from the Xeomin group "switched" into the group with less severe spasticity (< 2 points according to the modified Ashworth Scale). The obtained clinical data fully corresponded to the dynamics of electromyographic parameters as a decrease in the amplitude and area of M-responses of the target muscles (lateral and medial heads of the gastrocnemius muscle), a decrease in the ratio of the amplitudes of M-responses both from the lateral head of the gastrocnemius muscle and the tibialis anterior muscle, and from the medial head of the gastrocnemius muscle and tibialis anterior muscle. The absence of significant differences with the comparison group in all clinical parameters proved the similar clinical efficacy of Xeomin and Botox in the treatment of gastrocnemius muscle spasticity in children with CP, which was confirmed by unidirectional changes in electromyographic parameters in both groups of patients. Treatment with Xeomin under the proposed study protocol was safe and well tolerated by patients. Adverse events (AEs) were only mild or moderate in severity and were observed in 9.4 % of cases in patients from the Xeomin group and in 6.3 % of cases in patients from the Botox group. Therefore, the study results allow us to consider Xeomin as a safe product for the treatment of spasticity in children with CP aged 2 to 12 years [18].

The clinical safety of Xeomin in CP was also evaluated in two specifically designed studies. A randomized, double-blind study by Italian authors compared the safety profiles of incobotulinumtoxinA (Xeomin) and onabotulinumtoxinA (Botox) in 35 patients with hemiparetic CP (18 children) and spastic diplegia (17 children) aged 3 to 18 years. The gastrocnemius dose for both products was 5 U/kg body weight. The study results showed the same safety profile for the studied BTA products with mild to moderate AEs that spontaneously resolved without special treatment [19].

Another open-label prospective study with repeated injections of incobotulinumtoxinA in a large group of patients with CP (69 children, mean age of 8.3±4.0 years) was designed to study the safety profile [20]. The study included children with different scores (level I to level V) according to the Gross Motor Function Classification System (GMFCS). The average number of injection procedures was 2.8±1.5 (maximum number: 6); and the average interval between injections was 6.0±1.7 months. A tiered approach was used for botulinum toxin therapy, i. e. the number of injected muscles per procedure ranged from 2.4±1.2 in the first cycle to 4.2±1.9 in the sixth cycle of injections. In this case, the average total dose of incobotulinumtoxinA varied from 191.7±126.2 U in the first cycle to 368.0±170.0 U in the sixth cycle of injections, and the dose varied from 8.5±5.4 to 9.9±5.5 U/kg body weight. The following muscle groups were most often injected: gastrocnemius (68.1 %), leg flexor group (47.8 %), adductor longus (42 %). The incidence of AEs was observed at 37.5 % of injections. The most common AE was injection site pain. Only muscle weakness and fever were considered treatment-related AEs. In general, according to the authors, treatment with incobotulinumtoxinA injections was assessed as well-tolerated [20].

The efficacy of incobotulinumtoxinA in CP was thoroughly evaluated in several specifically designed international clinical studies [6, 7, 21].

To study the effect of Xeomin therapy on motor function, a phase 3, prospective, multicenter, randomized, double-blind, parallel-group study (Treatment with IncobotulinumtoxinA in Movement, TIM) was conducted [6]. This made it possible to study the efficacy and safety of IncobotulinumtoxinA in patients aged 2 to 17 years (n=311) with CP and lower limb spasticity in three parallel groups using different total doses (4 U/kg body weight, but not more than 100 U; 8 U/kg body weight, but not more than 200 U; 16 U/kg body weight, but not more than 400 U) for two injection cycles performed in the range from 12 to 36 weeks. In bilateral CP, the total dose was distributed equally between the right and left sides and was injected into at least two muscles that flex the foot and form the equinus foot position (gastrocnemius, soleus, tibialis posterior, flexor digitorum longus, flexor hallucis longus). In unilateral

[1] Instruction for Medical Use of Xeomin is available at: *https://grls.rosminzdrav.ru*

CP, the total dose was distributed equally between at least two muscles that flex the foot and form the equinus foot position (gastrocnemius, soleus, tibialis posterior, flexor digitorum longus, flexor hallucis longus) and knee flexors (semitendinosus, semimembranosus, biceps femoris, gracilis) or hip adductors (gracilis; longus, brevis, magnus). A significant decrease in muscle tone, as assessed by the Ashworth Scale, was demonstrated 4 weeks after injections of incobotulinumtoxinA in each of the groups of patients receiving a different total dose of the product, both after the first and the second injection cycle [6]. Significant improvement was also identified according to the Global Impression of Change in Foot Flexor Spasticity. An additional assessment using the 66-item Gross Motor Function Measure (GMFM-66) showed that patients' motor function had improved in all three treatment groups from the end of the first injection cycle to the end of the study: an average increase in GMFM-66 score from 1.8±2.8; 1.2±3.5 and 1.4±3.1 to 3.1±3.4; 3.3±4.5 and 2.8±4.1 was reported among those who received incobotulinumtoxinA at a total dose of 4, 8, or 16 U/kg body weight (maximum 100, 300, or 400 U), respectively. There was also a favorable safety and tolerability profile in all study groups using different total doses of incobotulinumtoxinA over two injection cycles: no new or unexpected safety concerns; no serious treatment-related AEs; only one patient discontinued from the study due to AE; no cases of secondary non-response due to neutralizing antibody formation.

To study the effect of Xeomin therapy on the long-term safety and motor function, a phase 3, open-label, prospective, multicenter study (Treatment with IncobotulinumtoxinA in Movement Open Label, TIMO) was conducted [7]. This made it possible to study the long-term safety and efficacy of incobotulinumtoxinA in patients (n=370) aged 2 to 17 years with CP and lower and upper limb spasticity using different total doses (8 U/kg body weight, but not more than 200 U for equinus foot position in bilateral and unilateral CP; for hip adduction position or knee flexion position in unilateral CP; 4 U/kg body weight, but not more than 100 U for upper limb spasticity; the maximum dose of 500 U was used only in GMFCS I–III patients) over four repeated injection cycles performed in the range from 12 to 16 weeks. Some patients from the TIM study continued to be treated with incobotulinumtoxinA in the TIMO study, which made it possible to analyze the results of six repeated injection cycles. A significant persistent decrease in muscle tone, as assessed by the Ashworth Scale, and an improvement according to the Global Impression of Change in Foot Flexor Spasticity were shown after all four injection cycles [7]. There was also a decrease in spasticity in other lower and upper limb muscles, as assessed by the Ashworth Scale and the Global Impression of Change Scale. When evaluating the results of six repeated injection cycles, it was noted that each repeated injection of incobotulinumtoxinA resulted in an even greater decrease in muscle tone. This is especially evident for foot flexors and hip adductors. An additional assessment using GMFM-66 showed an improvement over baseline: 53.9±18.9 (by 1.5±3.2; 2.6±4.0 and 3.8±5.1 points at the beginning of the second, third and fourth injection cycle, respectively, and by 4.8±5.9 points at the final visit), which indicates an increase in motor functions in children with long-term use of incobotulinumtoxinA for CP. A favorable safety and tolerability profile was demonstrated over four injection cycles. No patient previously treated with BTA products showed neutralizing antibodies after treatment with incobotulinumtoxinA, and no patient had secondary non-response due to neutralizing antibodies.

The efficacy and safety of incobotulinumtoxinA for the treatment of upper limb spasticity in children with CP was evaluated in a specifically designed clinical study XARA (IncobotulinumtoxinA in Arm Treatment in Cerebral Palsy), which included a double-blind phase (one injection cycle) in three parallel groups using different total doses (2 U/kg body weight per upper limb, but not more than 50 U, a total of 2 U/kg body weight or 100 U for both arms; 6 U/kg body weight per upper limb, but not more than 150 U, a total of 12 U/kg body weight or 300 U for both arms; 8 U/kg body weight per upper limb, but not more than 200 U, a total of 16 U/kg body weight or 400 U for both arms) [21]. Patients could also be treated for lower limb spasticity if there was a clinical need for different doses depending on the therapeutic group: 1 U/kg body weight or 25 U; 3 U/kg body weight or 75 U; 4 U/kg body weight or 100 U, respectively. After the double-blind phase, the patients continued treatment in the open-label phase, which included three additional injection cycles at a total dose of 8 U/kg body weight per upper limb, but not more than 200 U, a total of 16 U/kg body weight or 400 U for both arms. The maximum total dose (including injections into the lower limb muscles) did not exceed 20 U/kg body weight or 500 U and was used only in GMFCS I–III patients. Patients in all treatment groups were found to achieve a clinically significant decrease in muscle tone. The changes were more significant in the high incobotulinumtoxinA dose group than in the low dose group (p=0.0099). All treatment groups achieved a clinically significant improvement according to the Global Impression of Change in Spasticity. In the open-label phase, a significant decrease in muscle tone was consistent and sustained throughout all three repeated injection cycles. For some patterns of spasticity (elbow flexion, wrist flexion, thumb in the palm), it was found that each repeated injection of incobotulinumtoxinA resulted in an even greater decrease in muscle tone as measured by the Ashworth Scale compared to the results in the high dose group (8 U/kg) in a double-blind phase. A favorable safety and tolerability profile was noted for unilateral and bilateral treatment with a total dose of up to 20 U/kg body weight (500 U). None of the patients not treated with other BTAs prior to the XARA study showed neutralizing antibodies. In addition, none of the patients showed a decrease in the efficacy of treatment or the development of secondary resistance to treatment with incobotulinumtoxinA.

All the data presented above show the high efficacy and the most favorable safety profile of Xeomin (no secondary resistance; and none of the patients without previous treatment with BTA products had neutralizing antibodies after treatment with incobotulinumtoxinA) in the treatment of spasticity and excessive muscle tone of both the lower and upper limbs in patients with CP.

Efficacy and safety of IncobotulinumtoxinA for the treatment of sialorrhea in patients with CP

In 2021, a new indication of Xeomin for "chronic sialorrhea in children aged 2 to 18 years" was approved in Russia. This was done based on the results of a prospective, random-

ized, double-blind, placebo-controlled, multicenter, parallel-group study with an open-label extension period (Sialorrhea Pediatric Xeomin Investigation, SIPEXI) [14]. In most patients included in this study, sialorrhea was caused by CP. The main group consisted of children aged 6 to 17 years. The study was divided into two parts: the main period, including screening and double-blind phase (first injection), and the open-label period (three additional repeated injections). After enrollment and randomization, one third of patients (72 children) received placebo injections and two thirds (148 children) received incobotulinumtoxinA. Injections were made in the parotid and submandibular glands on both sides with ultrasonic guidance in a total dose calculated based on the child's body weight, but not more than 75 U per procedure. The double-blind phase results showed a significant decrease in saliva production in the incobotulinumtoxinA injection group compared to the placebo group at 4, 8, 12 and 16 weeks post injection. The assessment was carried out using a quantitative method to measure the unstimulated saliva flow rate. Similar changes were obtained when analyzing the Global Impression of Change Scale. The open-label study period results were even more striking: each subsequent injection of incobotulinumtoxinA was accompanied by greater changes in both the unstimulated saliva flow rate and the Global Impression of Change Scale. This led the study authors to conclude that the use of repeated injections may be reasonable to achieve a long-term improvement in children with sialorrhea. The safety profile of incobotulinumtoxinA was favorable with a low overall incidence of AEs, with no serious treatment-related AEs reported in any case. There were also no significant differences in the incidence of AEs between the placebo group and the incobotulinumtoxinA group.

The management of hypersalivation (chronic sialorrhea) in CP is quite relevant, since, according to various authors, this condition occurs in 10–38 % of cases and has serious medical complications, involves a psychosocial burden for patients and their families, which has a significant negative impact on the quality of life. Despite the variety of therapeutic approaches (oral medications, special mucoadhesive patches, oral motor exercises and oral sensorimotor therapy, behavior therapy, surgical treatment), there is still no optimal solution. With the advent of botulinum therapy, the immediacy of the problem of chronic sialorrhea in CP can be significantly reduced [22].

Summary of the results of a Russian retrospective study on the treatment of spasticity and sialorrhea in CP

Using one BTA product for correction of two severe pathological conditions (spasticity and sialorrhea) in spastic CP in one injection session is a reasonable and promising approach. However, there are currently no recommendations that could clearly regulate the therapeutic strategy of doctors during botulinum therapy for the simultaneous treatment of spasticity and sialorrhea. Last year, the results of a retrospective multicenter study on the use of incobotulinumtoxinA for the treatment of spasticity and sialorrhea in CP in real clinical practice were published in Russia [23]. The choice of incobotulinumtoxinA as a BTA product was reasonable since it is the only product with official indications for the treatment of spasticity and sialorrhea in children in the Instruction for Medical Use. A large number of patients included in the retrospective analysis made it possible to:

1) calculate the average total doses of incobotulinumtoxinA used to treat children with spastic CP;
2) calculate the average total doses of incobotulinumtoxinA used to treat sialorrhea in children with CP;
3) calculate the average total doses of incobotulinumtoxinA used in the simultaneous treatment of spasticity and sialorrhea in CP;
4) determine the frequency of incobotulinumtoxinA injections into the most common target muscles of the lower and upper limbs in patients with CP;
5) calculate the average doses (U and U/kg body weight) of incobotulinumtoxinA for the most common target muscles of the lower limbs.

Consensus guidelines on the use of incobotulinumtoxinA for the treatment of spasticity and sialorrhea in patients with CP

Using the results of a Russian retrospective multicenter study on the use of incobotulinumtoxinA for the treatment of spasticity and sialorrhea in CP, data from recently published international clinical studies, and our own clinical experience, we have developed the consensus guidelines on the use of incobotulinumtoxinA for the treatment of spasticity and sialorrhea in patients with CP. These guidelines include:

- practical guidelines on calculation of the total dose of incobotulinumtoxinA per procedure for the treatment of spasticity in CP;
- practical guidelines on calculation of the incobotulinumtoxinA dose for the most common target muscles of the lower and upper limbs when injected for the treatment of spasticity in CP;
- practical guidelines on dilution and calculation of incobotulinumtoxinA doses for the treatment of sialorrhea in children;
- practical guidelines on dilution and calculation of incobotulinumtoxinA doses for the simultaneous treatment of spasticity and sialorrhea in CP.

Practical guidelines on calculation of the total dose of incobotulinumtoxinA per procedure for the treatment of spasticity in CP

The total dose of incobotulinumtoxinA per procedure for the treatment of spasticity in CP depends on the number of potential target muscles and the dose for each muscle. For a child weighing up to 25 kg, it is preferable to calculate doses per 1 kg of body weight, and for a child weighing more than 25 kg, to take into account the maximum recommended doses for a particular muscle or group of muscles that constitute a certain pathological pattern. For example, if injections only into the gastrocnemius muscles on both sides were required for spastic diplegia, the total dose per procedure will be equal to the sum of doses for each of the gastrocnemius muscles. For multilevel spasticity, the total dose will be much higher and will also be equal to the sum of doses for each target muscle included in the injection protocol, but the maximum total dose per procedure in these cases should not exceed 20 U/kg body weight or 500 U. For GMFCS IV–V patients with risk factors for serious AEs (severe dysphagia, history of aspiration

syndrome, respiratory disorders), the maximum total dose of incobotulinumtoxinA should not exceed 16 U/kg body weight or 400 U. If multilevel injections into the lower and upper limb muscles are required, it is important to determine the priorities of botulinum therapy by considering the general concept of the child rehabilitation and particular immediate treatment goals, but still the total dose per procedure should not exceed 20 U/kg body weight or 500 U, which will provide the optimal safety profile.

Practical guidelines on calculation of the incobotulinumtoxinA dose for the most common target muscles of the lower and upper limbs when injected for the treatment of spasticity in CP

Since the Instruction for Medical Use of Xeomin indicates the recommended doses only for the gastrocnemius muscles, the results of a Russian retrospective multicenter study on the use of incobotulinumtoxinA for the treatment of spasticity and sialorrhea in CP were further used as the basis for practical guidelines [23]. After a clinical examination of a child with CP and the determination of a pathological motor pattern, the target muscles for the botulinum therapy procedure should be selected. The dose for a particular target muscle may depend on several factors: the child's age and body weight, the degree of increase in muscle tone and the level of spasticity, treatment goals and priorities, GMFCS level, risk of secondary orthopedic complications, etc. Tables 1 and 2 show the doses of incobotulinumtoxinA (median, interquartile range, minimum and maximum values), which may be the basis for the choice when performing multilevel botulinum therapy in children with spastic CP. IncobotulinumtoxinA doses have been intentionally recalculated for this publication as the interquartile range contains the "central" 50 % of the characteristic values and doses ranging between the 25th and 75th percentiles were most frequently used by participants of the Russian retrospective multicenter study for effective treatment of spasticity in CP. Table 1 is more convenient to use in the treatment of children with body weight < 25 kg since the doses are indicated per 1 kg/body weight. With a child's body weight > 25 kg, it is preferable to use Table 2 where the doses of incobotulinumtoxinA for a particular muscle are given in U. It is reasonable to use repeated cycles of incobotulinumtoxinA injections (at least six), which will provide long-term improvement and adequate control in lower and upper limb spasticity in patients with CP.

Practical guidelines on dilution and calculation of incobotulinumtoxinA doses for the treatment of sialorrhea in children

If a child has chronic sialorrhea, then, regardless of its cause, it is possible to use botulinum therapy to correct excessive salivation. For this purpose, incobotulinumtoxinA is injected into the parotid and submandibular glands on both sides. In this case, the ratio of the product injected into the parotid and submandibular glands on both sides should be 3:2. All salivary gland injections must be ultrasound-guided. The product is reconstituted by introducing an isotonic solution of sodium chloride (0.9 % solution) into the vial. For the treatment of sialorrhea, it is recommended to use a solution at a concentration of 2.5 U/0.1 mL. To obtain such a solution, inject 4.0 mL of isotonic sodium chloride solution into the vial containing 100 U, and inject 2.0 mL of isotonic sodium chloride solution into the vial containing 50 U. IncobotulinumtoxinA doses for injection into the salivary glands in chronic sialorrhea are determined depending on the

Table 1. *IncobotulinumtoxinA doses (U/kg body weight) for target muscles of the lower and upper extremities, used for injections in patients with spastic CP*

Muscles	n	Median	25th; 75th percentiles	Min–max
Legs				
Gastrocnemius	214	4.9	3.1; 7.0	0.6–11.4
Semitendinosus/semimembranosus	180	3.4	2.5; 4.4	0.6–9.0
Gracilis	167	2.9	2.1; 3.4	0.5–6.7
Adductor longus/magnus/brevis	166	3.1	2.6; 4.0	0.5–8.8
Rectus femoris	66	2.2	1.9; 3.2	0.7–5.0
Soleus	44	1.5	1.1; 1.9	0.4–3.2
Iliopsoas	42	2.9	2.2; 3.7	1.0–5.4
Tibialis posterior	24	1.7	1.1; 2.6	0.7–4.2
Arms				
Pronator teres	189	1.2	0.9; 1.7	0.2–3.8
Biceps brachii	112	1.4	1.0; 2.2	0.2–4.4
Adductor pollicis	100	0.5	0.4; 0.8	0.1–1.6
Brachialis	98	1.4	1.0; 2.2	0.2–4.2
Brachioradialis	66	0.9	0.6; 1.6	0.2–2.8
Flexor carpi radialis	35	0.7	0.5; 0.9	0.4–1.7
Triceps brachii	27	1.9	1.4; 2.4	0.7–3.0
Flexor digitorum sublimis	26	1.0	0.6; 1.6	0.3–2.7
Pectoralis major	24	1.0	0.8; 1.4	0.5–3.2
Flexor carpi ulnaris	12	0.5	0.4; 0.8	0.2–1.4
Flexor digitorum profundus	11	0.5	0.4; 0.7	0.3–0.7
Teres major	10	0.7	0.6; 1.0	0.4–3.8

Table 2. *IncobotulinumtoxinA doses (U) for target muscles of the lower and upper extremities, used for injections in patients with spastic CP*

Muscles	n	Median	25th; 75th percentiles	Min–max
Legs				
Gastrocnemius	214	72.5	50.0; 100.0	15–250
Semitendinosus/semimembranosus	180	50.0	40.0; 70.0	10–220
Gracilis	167	40.0	30.0; 50.0	5–100
Adductor longus/magnus/brevis	166	50.0	30.0; 60.0	15–200
Rectus femoris	66	37.5	20,0; 60,0	10–80
Soleus	44	25.0	20.0; 40.0	10–80
Iliopsoas	42	40.0	30.0; 50.0	10–80
Tibialis posterior	24	40.0	30.0; 50.0	10–60
Arms				
Pronator teres	189	20.0	15.0; 30.0	5–100
Biceps brachii	112	25.0	20.0; 40.0	5–120
Adductor pollicis	100	10.0	5.0; 10.0	5–25
Brachialis	98	21.25	20.0; 30.0	5–60
Brachioradialis	66	17.5	10.0; 30.0	5–40
Flexor carpi radialis	35	10.0	10.0; 20.0	5–40
Triceps brachii	27	20.0	15.0; 30.0	10–40
Flexor digitorum sublimis	26	15.0	10.0; 20.0	5–30
Pectoralis major	24	20.0	12.5; 22.5	10–40
Flexor carpi ulnaris	12	15.0	7.5; 25.0	5–30
Flexor digitorum profundus	11	10.0	10.0; 15.0	5–20
Teres major	10	15.0	15.0; 25.0	10–50

Table 3. *IncobotulinumtoxinA doses for injection into the salivary glands in chronic sialorrhea*

Weight, kg	Parotid gland		Submandibular gland		Total dose
	total dose per gland, U	solution volume, mL	total dose per gland, U	solution volume, mL	(salivary glands on both sides)
⩾ 12, but < 15	6	0.24	4	0.16	20
⩾ 15, but < 19	9	0.36	6	0.24	30
⩾ 19, but < 23	12	0.48	8	0.32	40
⩾ 23, but < 27	15	0.60	10	0.40	50
⩾ 27, but < 30	18	0.72	12	0.48	60
⩾ 30	22.5	0.90	15	0.60	75

child's body weight (Table 3). For children weighing ⩾ 30 kg, the same total dose of 75 U is injected into four salivary glands (parotid and submandibular on both sides). For children weighing < 12 kg, incobotulinumtoxinA is not recommended for the treatment of chronic sialorrhea. The given doses of incobotulinumtoxinA showed high efficacy and safety in a prospective, randomized, double-blind, placebo-controlled, multicenter, parallel-group study with an open-label extension period (SIPEXI) [14]; therefore this particular protocol is recommended. It is reasonable to perform a course of at least four repeated injection cycles, which will provide long-term improvement and adequate control of chronic sialorrhea in children.

Practical guidelines on dilution and calculation of incobotulinumtoxinA doses for the simultaneous treatment of spasticity and sialorrhea in CP

The maximum total dose per incobotulinumtoxinA injection procedure in the simultaneous treatment of spasticity and sialorrhea in CP should not exceed 20 U/kg body weight or 500 U. For GMFCS IV–V patients with risk factors for serious AEs (severe dysphagia, history of aspiration syndrome, respiratory disorders), the maximum total dose of incobotulinumtoxinA should not exceed 16 U/kg body weight or 400 U. The proportion of the product required for the treatment of sialorrhea from the total dose per procedure is calculated depending on the child's body weight (see Table 3) and never exceeds 75 U. For example, for a child with CP, spastic diplegia, GMFCS III, body weight of 30 kg, the maximum total dose of incobotulinumtoxinA for multilevel antispasmodic treatment and correction of sialorrhea would be 500 U. 75 U of them must be injected into the salivary glands, and 425 U must be used to treat spasticity. In this case, a solution at a concentration of 2.5 U/0.1 mL should be used for the treatment of chronic sialorrhea, and a solution at a concentration of 5 U/0.1 mL is commonly used for the treatment of spasticity. The treatment of spasticity and sialorrhea in a single injection procedure allows to reduce intervals between repeated injection cycles and also demonstrates a good efficacy and safety profile of a long-term use of incobotulinumtoxinA.

Prospects for the use of incobotulinumtoxinA in CP

Recently, a large number of studies have been devoted to the development of pain syndrome in patients with CP due to long-term spasticity. It has been shown that the use of BTA products can be effective in the treatment of pain in CP [24]. Recently published studies have shown that incobotulinumtoxinA may reduce pain associated with spasticity in both the upper and lower limbs of patients with CP [21]. In the future, it is recommended to conduct specific studies to evaluate the analgesic effect of BTA products, including incobotulinumtoxinA, in spastic CP.

The systematic review by I. Novak et al. [4] presents the results showing that BTA products are effective in the treatment of dystonia in CP. Publications are available on the use of incobotulinumtoxinA for the treatment of various dystonic disorders in children [25]. Major studies on the efficacy and safety of incobotulinumtoxinA in secondary dystonic disorders in CP and other forms of primary and secondary dystonia are required.

Conclusion

The article presents the general consensus of the Russian specialists working with CP patients and using incobotulinumtoxinA (Xeomin) in their practice for the treatment of spasticity and sialorrhea. This consensus is based on the results of the Russian retrospective multicenter study on the use of incobotulinumtoxinA for the treatment of spasticity and sialorrhea in CP, data from recently published international clinical studies, and our own clinical experience. The detailed practical guidelines are presented on calculation of the total dose of incobotulinumtoxinA per procedure for the treatment of spasticity in CP, on calculation of the dose of incobotulinumtoxinA for the most common target muscles of the lower and upper limbs during the injection procedure for the treatment of spasticity in CP, on dilution and calculation of incobotulinumtoxinA doses for the treatment of sialorrhea in children, on dilution and calculation of incobotulinumtoxinA doses for the simultaneous treatment of spasticity and sialorrhea in CP. In order to treat spasticity and sialorrhea, it is optimal to use incobotulinumtoxinA, which allows to reduce intervals between repeated injection cycles and also demonstrates a good efficacy and safety profile for a long-term use. When planning injections into the target muscles for off-label indications, the judgement of the medical board and signing of the informed consent by the parent or legal representative of the patient are required.

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