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Review

# Botulinum toxin therapy in children with neurogenic detrusor overactivity

Jasmin Katrin Badawi

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## ABSTRACT

Special birth defects and neurological diseases can cause neurogenic detrusor overactivity (NDO). First-line pharmacotherapy is the antimuscarinic therapy, which can be limited by side effects or non-effectiveness. Therefore, pharmacological treatment of NDO in children includes off-label use of intravesical injections of botulinum toxin type A (BTA). In this review article, various clinical studies in which BTA was used for the treatment of NDO of different etiologies in children are discussed, including studies about children with acquired NDO. An electronic literature search was performed using PubMed, and studies published prior to March 2019 are reported. BTA injections are a clinically and urodynamically effective and safe treatment for NDO in children. The treatment is also important in protecting the upper urinary tract from damage and improving concomitant bowel dysfunctions. Fibrotic, acontractile bladders with poor bladder compliance and/or a very small initial bladder capacity and/or the presence of an open bladder neck all contributed to poor responses. A combined injection into the detrusor and external urethral sphincter may improve the clinical outcome in the detrusor–sphincter dyssynergia. New application methods are promising, such as the electromotive drug administration, to avoid general anesthesia. Furthermore, the minimal clinically effective dosage, inclusion criteria, and prognostic factors remain to be established.

**Keywords:** Acquired neurogenic detrusor overactivity; botulinum toxin type A injection; children; electromotive drug administration; EMDA; neurogenic detrusor overactivity.

## Introduction

Special birth defects, such as myelomenigocele, and a variety of neurological diseases, such as central nervous system tumors or trauma, can cause neurogenic detrusor overactivity (NDO). First-line pharmacotherapy is the antimuscarinic therapy, which is often limited by ineffectiveness or side effects. Therefore, pharmacological treatment of NDO in children includes off-label use of botulinum toxin type A (BTA), mainly applied as injections into the detrusor muscle. BTA is a neurotoxin produced by *Clostridium botulinum*. It inhibits the release of acetylcholine at the neuromuscular junction and also influences the afferent pathways of the micturition reflex by inhibiting the release of neurotransmitters.[1,2] The treatment of neurogenic and non-neurogenic DO improves clinical symptoms, such as urinary incontinence, and it is also important in protecting the upper urinary tract from damage. Two preparations of BTA are commonly used:[3] Botox (onabotulinum toxin A) and Dysport (abobotulinum toxin A). They are not interchangeable.[4,5]

## Material and methods

In March 2019, an electronic literature search was performed using PubMed. The following search terms were combined: "children," "toxin," and "detrusor overactivity." In addition, instead of "detrusor overactivity," the terms "detrusor hyperreflexia" or "neurogenic bladder" were used to find additional articles using different terminology. First, the identified titles and abstracts were screened. Then the full text was screened.

The following studies were excluded:

1. Where no clinical outcome was reported,
2. Where BTA was only injected into the sphincter,

**ORCID ID of the author:**
J.K.B. 0000-0002-1660-8008.

Medical Faculty Mannheim of the Ruprecht-Karls-University of Heidelberg, Mannheim Germany

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**Corresponding Author:**
Jasmin Katrin Badawi
E-mail:
jkb.ch@bluewin.ch



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**Table 1. Publications about children in which injections were used to apply botulinum toxin**

| Publication: first author`s surnname et al. | Year of publication | Number of children | Etiology of the bladder dysfunction (n: number of patients in case of subgroups) | Average age [year] or median age [year] |
|---|---|---|---|---|
| Schulte-Baukloh[9] | 2002 | 17 | MMC | 10.8 |
| Schulte- Baukloh[10] | 2003 | 20 | MMC (16), intraspinal astrocytoma (2), trauma (1), unknown (1) | 12.2 |
| Lusuardi[11] | 2004 | 15 | MMC | 5.8 |
| Schulte-Baukloh[12] | 2005 | 10 | MMC | 11.2 |
| Marte[13] | 2005 | 7 | MMC | 9.8 |
| Kajbafzadeh[14] | 2006 | 26 | MMC | 6.9 |
| Altaweel[15] | 2006 | 20 | MMC | 13 |
| Neel[16] | 2007 | 23 | MMC | 5.6 |
| Akbar[17] | 2007 | 19 | Myelodysplasia | 9.87 |
| Dobremez[18] | 2008 | 6 | Acquired neurogenic bladder | 11.6 |
| Neel[19] | 2008 | 10 | MMC | 5.9 |
| Do Ngoc Thanh[20] | 2009 | 7 | Different birth defects or acquired diseases (for details, see manuscript) | 10.2 |
| Safari[21] | 2010 | 60 | MMC | 6.58 versus 6.71 |
| Neel[22] | 2010 | 13 | MMC | 5.3 |
| Deshpande[23] | 2010 | 7 | Spina bifida | 16 |
| Romero[24] | 2011 | 12 | MMC (9), spinal cord injury (1), neonatal spinal cord infarction (1), posterior urethral valves (1) | Median age: 12.6 |
| Horst[25] | 2011 | 11 | MMC | 6.7 |
| Sager[26] | 2011 | 12 | myelomeningoceles, tethered cord, medullary astrocytoma, Ewing's sarcoma | 12.7 |
| Pascali[27] | 2011 | 24 and 24 | Group new needle*: spina bifida (17), SCI (5), others (cerebral palsy, myelitis; 2) Group standard needle*: spina bifida (16), SCI (4), others (cerebral palsy, myelitis; 4) | 7.8* and 8.2* (control group) |
| Le Nué[28] | 2012 | 8 | Acquired neurogenic bladder due to traumaticparaplegia or quadriplegia, perinatal stroke, neonatal ischemic anoxia, or post-spine surgery paraplegia | 12.4 |
| Zeino[30] | 2012 | 28 | MMC | 10.7 |
| Marte[31] | 2012 | 47 | MMC | 10.7 |
| Kim[32] | 2014 | 37 | spina bifida (29), syrinx (1), cerebral palsy (4), Guillain–Barré syndrome (1), spinal cord hemangioma (1), postmeningitis sequelae (1) | 7.49 |
| Dariane[33] | 2014 | 16 | Spinal cord lesions | |
| Figueroa[34] | 2014 | 17 | Spina bifida/spinal dysraphism, tethered cord | 10.7 |
| Sager[35] | 2014 | 26 | MMC, Ewing`s sarcoma, cord astrocytoma or tethered spinal cord | 13.3 |

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**Table 1. Publications about children in which injections were used to apply botulinum toxin (continued)**

| Publication: first author`s surnname et al. | Year of publication | Number of children | Etiology of the bladder dysfunction (n: number of patients in case of Subgroups) | Average age [year] or median age [year] |
|---|---|---|---|---|
| Kask[36] | 2014 | 17 | MMC (12*), caudal regression (2), lipomyelomeningocele (1), diastematomyelia (1), sustained spinal trauma (1) | 11 |
| Tarcan[37] | 2014 | 31 | MMC | 7.95 |
| Tiryaki[38] | 2015 | 16 | MMC | Median age: 9 |
| Khan[39] | 2016 | 22 | MMC (10), anorectal malformation (3), spinal cord trauma (3), tethered cord syndrome (2), caudal regression syndrome (2), sacrococcygeal teratoma (1), transverse myelitis (1) | 10 |
| Greer[40] | 2016 | 20 out of 53: NDO | MMC, others (see manuscript) | Median age of the whole group: 8 |
| Sekerci[41] | 2018 | 19 | myelodysplasia | 10.3 |
| Hascoet[42] | 2018 | 53 | open and closed spinal dysraphisms | 8.5 |

*information obtained by the corresponding author; SCI: spinal cord injury; MMC: myelomeningocele

**Table 2. Publications about children in which EMDA was used to apply botulinum toxin**

| Publication: first author`s surname et al. | Year of publication | Number of children | Etiology of the bladder dysfunction | Average age [year] |
|---|---|---|---|---|
| Kajbafzadeh[44,45] | 2011 | 15 | MMC | 7.8 |
| Kajbafzadeh[46] | 2016 | 16 | MMC | 8.4 |
| Ladi-Seyedian[47] | 2017 | 24 | MMC | 9 |

MMC: myelomeningocele; EMDA: electromotive drug administration

3. Those regarding idiopathic/non-neurogenic detrusor overactivity
4. Where only adults were treated,
5. Review articles [6] and consensus reports.

Published studies that were included are presented in the chronological order. Randomized and non-randomized studies, as well as retrospective and observational studies, are included in this review, since the number of studies on the subject is rare, and important information about the subject would be ignored by focusing only on randomized (prospective) studies. A variety of methodological quality assessment tools for different types of clinical studies are available. There is no consensus concerning the best tool to use.[7,8]

Furthermore, even these tools remain subjective. Therefore, no quality assessment tool was used. If a piece of required information (e.g., about etiologies of the neurogenic bladder dysfunctions) was not available in the original publication, the corresponding author was contacted in writing and asked about the required information.

## Results

Fifty-three articles were initially found using the terms "detrusor overactivity," "children," and "toxin" and six articles using "detrusor hyperreflexia," "children," and "toxin," respectively. Using the terms "neurogenic bladder," "children," and "toxin," 119 publications were initially found. After exclusion using the above-mentioned exclusion criteria, 33 studies in which botulinum toxin was injected into the detrusor muscle of children with NDO could be included (Table 1).

Three studies, in which botulinum toxin was applied by electromotive drug administration (EMDA), were included, too (Table 2). Since the study design differ among all studies, the urodynamic and clinical outcomes are presented inside the text, allowing the reader to be informed first about the study design. These values are not additionally shown in the table form, which would suggest a direct comparability of the clinical and urodynamic outcomes, which is not really the case. Additionally cited publications allow one to understand the scientific context.

## Discussion

The first study about the treatment of children with NDO due to myelomeningocele (MMC) by injections of BTA into the detrusor was published in 2002.[9] Seventeen children [average age (AA): 10.8 years] using clean intermittent catheterization (CIC)

received 85 to 300 units of BTA into 30 to 40 sites of the detrusor muscle. The effectiveness was urodynamically proven.

The maximal bladder capacity (MBC) significantly increased by 57%, from 138 to 215 mL. The maximum detrusor pressure (MDP) significantly decreased by 33% from 59 to 40 $cmH_2O$. The compliance significantly increased by 122%, from 20 to 45 $mL/cmH_2O$.

In 2003, a study about 20 children with NDO was published.[10] Botox was injected into 30–50 sites. The dosage was 12 units/kg of body weight (maximum: 300 units). The MBC significantly changed from 163 mL before treatment to 220, 201, and 222 mL after 2–4 weeks, 3 months, and 6 months after the injection, respectively. The MDP changed from 60 $cmH_2O$ before the injection to 35, 47, and 62 $cmH_2O$ after the above-mentioned periods, respectively. A statistical significance was only given for the first value. The authors concluded that the effect of BTA lasted about 6 months.

Lusuardi et al.[11] investigated 15 children (AA, 5.8 years) suffering from a bladder dysfunction due to MMC. BTA was injected (dosage: from 10 U/kg up to a maximum of 360 U) into 25–40 sites of the detrusor. The follow-up time was 24 months. Urodynamic parameters and the continence improved: the average bladder reflex volume significantly increased from 72 to 298 mL. The MDP significantly decreased from 79 to 43 $cmH_2O$. MBC significantly increased from 136 to 297 mL. The detrusor compliance significantly increased from 18 to 51 $mL/cmH_2O$.

Ten patients became dry between CIC. The average efficacy and durability of the toxin was 10.5 months. The first results on the long-term effect of repeated injections were published in 2005.[12] The charts of 10 children (AA, 11.2 years) were reviewed. At least three Botox injections were applied. Urodynamic measurements were performed 6 months after each injection. The MDP decreased by 7% and 39% after the first and fifth injection, respectively, compared to the value before treatment. The MBC increased by 88% and 72%, respectively. Compliance showed no change after the first injection and an increase of 109% after the 5$^{th}$ injection. No major side effects were shown.

Marte et al.[13] investigated 7 children (AA, 9.8 years; age range, 5–17 years) with NDO due to MMC, being incontinent despite CIC. BTA was injected at a dosage of 200 IU in about 20 sites of the detrusor muscle. Leak point pressure did not significantly change. Leak point volume and the specific volume at the 20 $cmH_2O$ pressure significantly increased. One patient previously treated with a Cohen reimplantation technique experienced transient VUR, which resolved spontaneously within 1 month. No major side effects occurred.

Kajbafzadeh et al.[14] performed a prospective study that investigated 26 children with NDO (AA, 6.9 years) due to MMC, and not only the urological parameters, but also the bowel dysfunction. The evaluation was performed before the injection and 4 months after it (dosage, 10 IU/kg). Nineteen children became completely dry between CIC. The total improvement in UI was 88%. The average MDP was significantly decreased from 139 to 83 cm $H_2O$. The average MBC significantly increased from 103 to 270 mL. Fifteen patients had varying degrees of VUR before the procedure. Eleven of these children showed a decrease in the VUR grade. Interestingly, this study shows a positive effect on the concomitant bowel dysfunction in 10 of 15 patients.

In 2006, the effect of repeated BTA injections in 20 children (AA: 13 years) with neurogenic bladder due to MMC was investigated.[15] A dosage of 5 IU/kg (maximum: 300 IU) BTA was injected at 10–30 sites. After the first treatment, 13 children became continent. All urodynamic values significantly changed: MBC increased from 216 mL to 338 mL, MDP decreased from 43 to 22 cm $H_2O$, and the compliance increased from 5.2 to 13 mL/cm $H_2O$. At an average of 8.1 months after the first injection, the 13 children treated successfully received a second injection, which led to similar significant improvements. Among the responders, three received three injections, and one received four injections, all of whom exhibited improvements. Among the initial cohort of 20 children, 7 failed to improve initially, and six failed to improve after a second injection.

Neel et al.[16] compared the outcome of BTA injection alone versus a combination with oral therapy using oxybutynin chloride in a group of 23 children (AA: 5.6 years) with neurogenic bladder dysfunction after repair of a myelomeningocele, which was originally lumbar (n=15), lumbosacral (n=7), or sacral (n=1). The clinical and urodynamic outcomes were similar compared to other studies. None of the patients had side effects. The additional use of anticholinergics had no benefits.

Akbar et al.[17] showed no lack of efficacy of repeated injections in 19 children with neurogenic bladder due to myelodysplasia. A significant improvement in the bladder capacity, the detrusor pressure at maximum filling, and the detrusor compliance was shown after the first injection. After two additional injections, the treatment was still effective. No tachyphylaxis was shown. The follow-up time was at least 3 years.

In 2008, a report about six children with acquired neurogenic bladder was published.[18] The patients performed CIC and suffered from UI despite anticholinergics (AA: 11.6 years; range: 5–18 years). Their BC was lower than the capacity predicted for their age (average: 68%±32.8). BTA was injected into 20–30 sites of the detrusor muscle (dosage: 12 units/kg; maximum: 300 units). Postoperatively, UI occurred in one child only during UTIs. In four children, anticholinergic treatment could be

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stopped. Two months after treatment, all children showed normal detrusor pressures. The capacity was higher than the capacity predicted for age (113%±22).

In 2008, another prospective study [19] was published, in which the efficacy and durability of a combination of BTA injections (dosage: 12 U/kg; maximum: 300 U) and endoscopic treatment of VUR were investigated in children with non-compliant refluxing bladders due to MMC. All 10 children (AA: 5.9 years) did not respond to standard conservative therapy. They had VUR (bilateral in six patients). Submucosal injection of Deflux was performed with the first BTA treatment in six and with the second one in four patients, respectively. The grade of reflux was between grades III and V. MBC and MDP improved significantly (MBC: 79–155 mL; MDP: 55–37 cm $H_2O$). Fifteen out of 16 refluxing ureters were completely resolved. Of six incontinent patients, five reached complete dryness between catheterizations. Additionally, in one child, a partial improvement was shown.

In 2009, a retrospective study [20] of seven children suffering from NDO following birth defects or due to acquired diseases (malignant meningioma, myofibroblastic tumor, spinal cord astrocytoma, vertebral tuberculosis, lipoma of the conus medullaris, and sacral lipomyelomeningocele) was published. The total dosage of Botox ranged from 6 to 11 IU/kg (maximum: 300 IU). In three patients with bladder sphincter insufficiency, Deflux was additionally injected into the bladder neck. Up to five injections were applied. The maximum catheterized volume increased, MDP decreased, and the compliance increased. A VUR grade II present in one child resolved. UTI was the only adverse effect. The average interval between injections was 8.7 months.

In an interesting single-center, prospective, double-blind, and randomized study,[21] 60 children with bladder dysfunction due to MMC were investigated. The authors compared the injection of BTA (dosage: 10 U/kg) alone versus the intradetrusor injection of BTA (dosage: 8 U/kg) combined with the injection of BTA into the external urethral sphincter (dosage: 2 U/kg, injections at four sites). Better outcomes concerning incontinence, constipation, VUR, and creatinine level were shown for the group in which the urethral sphincter was additionally treated. Only in this group, a significant improvement in postvoiding residual volume was shown. This study suggests a combined injection of BTA into the detrusor muscle and the external urethral sphincter, when a detrusor–sphincter dyssynergia is present.

Another prospective study was published in 2010,[22] investigating a combination therapy of 13 children (AA: 5.3±2.5 years) with MMC and consecutive neurogenic bladder dysfunction, VUR (bilateral in seven children), and in most of the patients, stool incontinence. All children received an intradetrusor injection of BTA (dosage: 12 U/kg; maximum: 300 U). In addition, a submucosal Deflux injection was applied to treat VUR. In children who were still diaper dependent due to stool incontinence, the Peristeen anal irrigation system was used. Ninety-five percent of 20 refluxing ureters completely resolved, including one after the second attempt. Seven of eight urinary incontinent children attained complete dryness between catheterizations. In 10 of 13 patients, stool dryness was achieved using anal irrigation one to two times weekly.

The following study[23] showed a poor correlation between the improvement in the urodynamics and the subjective outcomes in seven children (median age: 16 years) with neurogenic bladder due to spina bifida. In five patients, a significant increase in bladder compliance and a significant improvement in incontinence at the one-month follow-up were shown. These beneficial effects in bladder compliance and incontinence dissipated by nine months. In two patients whose baseline bladder capacity was markedly reduced (<200 mL), the improvement was very minimal. No side effects were found.

In a prospective study[24] published 2011, 12 children were included. Eleven children suffered from NDO due to following etiologies: myelomeningocele (n=9), which was in one case associated with a cloaca syndrome, and in another case with an anorectal atresia, traumatic spinal cord injury (n=1), and neonatal spinal cord infarction (n=1). In one child, posterior urethral valves were the cause of the bladder dysfunction. This boy had a single ureterostomized kidney. In this patient, the indication for the injection of BTA into the detrusor muscle was to increase the capacity and compliance of the bladder prior to the closure of the ureterostomy. The dosage of Botox was 10 IU/kg (maximum: 300 IU). Up to two successive injections were performed. Urodynamic parameters improved after 4 weeks in 10 children, and after six months, the improvements decreased. Changes were similar after repeated injections.

Horst et al.[25] showed a positive temporary effect of BTA on detrusor pressure and BC in children with bladder dysfunction and poor bladder compliance due to myelomeningocele. Eleven children (AA: 6.7 years) were examined. Their average bladder compliance amounted to 7 mL/cm$H_2O$. The authors found that 3 months after the injection, the detrusor pressure decreased by 17%, and the bladder capacity increased by 33%. In one patient, the bladder compliance stayed poor. Twelve months later an effect was shown, but the improvements were smaller. After repeated injections, similar effects on capacity and detrusor pressure were shown. Bladder compliance normalized (defined as >20 ml/cm$H_2O$) only in one patient.

In 2011, a study that included 12 children with neurogenic bladder treated with intradetrusor BTA injections (dosage: 300 U) was published.[26] The following etiologies were found: myelomeningoceles, tethered cord, medullary astrocytoma, and Ew-

ing's sarcoma. After the first treatment, 50% of patients achieved complete continence, and 20% still suffered from minimal leaks. Urodynamic changes were not significant. After six months, 10 patients were reinjected.

Pascali et al.[27] compared the original injection technique of BTA (use of a rigid cystoscope and a 3.7 Fr standard flexible needle) with another technique using an N-DO endo-injector needle system. In one group including 24 children aged 3.8–17.5 years, BTA was injected into the detrusor and/or urethral sphincter using a rigid cystoscope and the new N-DO™ endo-injector needle system. In the other group, including 24 patients aged 3.6–17.8 years, BTA was injected with a 3.7 Fr standard flexible needle. The dosage of BTA was 10 IU/kg. Authors found a decrease of MDP and an increase of BC in both groups, which were not significantly different. No complications occurred. The operation time was shorter for the endo-injector needle technique, which may be an advantage when considering performing the operation under local sedation instead of using general anesthesia in older children.

In 2012, Le Nué et al.[28] reported about children (AA: 12.4 years) with acquired neurogenic bladder with DO due to traumatic paraplegia or quadriplegia, perinatal stroke, neonatal ischemic anoxia, or post-spine surgery paraplegia. One characteristic of acquired bladder diseases is a good initial bladder compliance. The authors retrospectively reviewed the clinical and urodynamic data of eight children treated by intradetrusor Botox injections over a 5-year period. The average MDP was 63 cm$H_2O$, and the MBC was 53% of the theoretical age-related value before treatment. The children received between 2 and 6 injections (average interval: 7 months). No adverse effects were found. The average continence score according to Nevéus et al.[29] was improved from 2.63 before to 0.3 after treatment. The average MDP significantly decreased from 63 to 22 and 31 cm $H_2O$ after one and two injections, respectively. The MBC increased from 53% to 91% and 109% after the 1st and 2nd injection (not statistically significant), and to 88% after the 3rd injection (statistically significant).

In 2012, a retrospective study[30] was published about 28 children with neurogenic DO due to MMC (AA: 10.7 years) treated with 10–12 U/kg of intradetrusor BTA (average follow-up: 48 months). The efficacy lasted 12 months (average). The urodynamic response was unchanged after several injections (average: 2.5 injections). Non-responders were found especially under the subgroup of children with severe low-compliance bladders.
Marte[31] performed a retrospective study on the BTA treatment of children with myelomeningocele. Forty-seven patients were included (AA: 10.7 years, range: 5-17 years). The children showed overactive/poor compliant neurogenic bladders on CIC, being resistant/non-compliant to pharmacological therapy. All children were incontinent, 10 of them showing concomitant monolateral/bilateral VUR, Grade II–IV. Most of the children received BTA. VUR was corrected in selected cases in the same session using 1–3 cc of subureteral Deflux. Seven patients remained stable, 21 patients required a second injection after 6–9 months, and 19 required a third one. No severe systemic complications occurred. Thirty-eight of the patients showed a slight hematuria for 2–3 days. Two children suffered from postoperative UTI. The results were promising: 38 children achieved dryness between CIC, and nine patients improved their incontinence, but still needed pads. Ten children have resumed anticholinergics. Urodynamically, a significant average increase in the leak point volume of 66.45% was found in all children.

To select the right patients for the intradetrusor BTA injection, it would be useful to have parameters predicting the outcome of the therapy. These parameters could be used to select special patients who could benefit from the therapy. For that purpose, Kim et al.[32] reviewed data of children (AA: 7.9 years) with NDO due to different etiologies (Table 1). In 37 children, a 1st BTA intradetrusor injection was performed. Urodynamic examination revealed a significant increase in MCC and residual urine volume. NDO persisted in only three children. Twenty patients were classified as responders and 17 as non-responders based on the Patient Global Impression of Improvement. Preoperative bladder compliance was significantly lower in non-responders. An open bladder neck (OBN) was found in nine cases, more likely in non-responders. It was found in a regression analysis that poor preoperative bladder compliance (<10 mL/cm $H_2O$) and the presence of an OBN were independent predictors of poor response after BTA injection.

Dariane et al.[33] reported on the endoscopic management of UI in children with neurogenic bladder due to spinal cord lesions. Of the 364 children followed for neurologic bladder, endoscopic management was performed in 22 with failure or intolerance related to first intention therapy. DO was found in 16 children, and sphincter deficiency in 13. The endoscopic procedures included one or several intradetrusor injections of BTA and/or dextranomer/hyaluronic acid (Dx/Ha) injection in the bladder neck. At the end of the average follow-up of 4 years, 16 children received 54 injections of BTA, and 13 children received 24 injections of Dx/Ha. Social continence was acquired quickly after injection. Injections had to be repeated every 8.7 (6–12) months. The morbidity was very low. After the 1st injection of Dx/Ha, 69% of the children significantly improved their incontinence score (from 1 to 0 or from 2 or 3 to 1 using the Schulte–Baukloh score), with better results for girls.

Figueroa et al.[34] treated children by intra-detrusor injections for congenital neuropathic bladder. Seventeen children (AA: 10.7 years; range: 3–17) underwent (repeated) BTA injections over a 4-year period. The following improvements in symptoms and

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urodynamic parameters were shown: average BC adjusted for age and compliance improved by 27% and 45% after the first injection, respectively. In three patients, in whom the maximum dose of BTA was reduced from 300 to 200 units, recurrent symptoms occurred, so authors have recommended 300 units as an optimal dosage. The overall patient/parental reported satisfaction rate amounted to 71%.

In a prospective study[35] published in 2014, the effects of repeated injections in 26 children with refractory NDO of different etiologies (MMC, Ewing`s sarcoma, cord astrocytoma, or tethered spinal cord) were examined. The AA was 13.3 years. BTA at a dose of 6.6 units/kg (maximum: 300 units) was injected into 45–60 sites. Twelve, six, and two patients were injected two, three, or four times, respectively. Fifty percent, 77%, and 75% of the patients were dry six months after the first, second, and third treatment, respectively. Compliance was significantly improved after the 1st injection. The MDP was not significantly changed. Cystoplasty was performed in five patients refractory to BTA injections, in four of them after one and in one patient after two BTA injections.

The efficiency of BTA injections in 17 children with NDO was investigated in 2014.[36] The clinical response and the urodynamic parameters were determined before and 1–3 months after the injection. Incontinence episodes were reduced in six out of 17 patients by >90%, and in three patients, a reduction of 50%–90% was found. The median duration of the response was 15 months. MDP significantly decreased from 45 to 32 $cmH_2O$. The number of patients with detrusor contractions during filling significantly decreased (12 versus 3). When poor bladder compliance was present before treatment, the duration of the response was short, or the patients did not respond at all. Bladder augmentation had to be performed in eight patients due to persistent incontinence.

In 2014, 31 children with NDO due to myelomeningocele (AA: 7.95 years) treated with intradetrusor injections of BTA (dosage: 10 U/kg; maximum: 300 U) were reported about.[37] Significant symptomatic and urodynamic improvements were found. The average duration of efficacy amounted to 28 weeks (single injection). The average time interval between injections amounted to 7 months.

Selecting patients who may benefit from BTA injection using parameters determined before injection would be very helpful to prevent unnecessary injections, especially because general anesthesia in younger children is needed for that procedure.

The following study revealed possible parameters[38]: the data of 16 children with MMC were reviewed. They had received intradetrusor BTA injections (10 units/kg). The authors classified the patients into two groups, based on urodynamic parameters: fibrotic bladders (non-compliant, acontractile, high pressures) or overactive bladders. Out of nine patients with DO five were completely dry between CIC after the initial treatment. In patients with DO, capacity and compliance increased significantly. In the seven patients with fibrotic bladders, no clinical and urodynamic improvements occurred.

Twenty-two children (AA: 10 years; range: 2–21) with medically refractory neuropathic bladder were reviewed retrospectively.[39] They were treated by intradetrusor BTA injections (dosage: 10 units/kg; maximum: 300 units). The mean follow-up was 11 months. The cause of neuropathic bladder was not only myelomeningocele (10 children), but also anorectal malformation, spinal cord trauma, tethered cord syndrome, caudal regression syndrome, sacrococcygeal teratoma, and transverse myelitis. No complications occurred. Twelve weeks after the procedure, the following urodynamic changes were found: cystometric BC significantly increased by 46%, which represented an increase from 60% to 87% of the age-expected capacity. The average MDP significantly decreased by 43% (from 63 to 44 $cmH_2O$), and the average compliance significantly improved by 104%. Pre-operatively, uninhibited detrusor contractions were found in 14 children; 10 resolved after the operation. Hydronephrosis was found in 10. It resolved in two and improved in one child. Fifty-four percent had improved continence after the initial injection, and 45% had achieved complete continence between catheterizations. The average duration of the improvement after one injection was only 4.6 months. In four patients, two or more injections had to be applied. In 50% of the patients in this study, urinary reconstructive surgery was performed before injection.

Another retrospective study including 53 children with a long-term follow-up of 10 years after injection was published in 2016.[40] The authors reported on the treatment of children (median age of the whole group: 8 years, range 1–18) with intravesical and intrasphincteric onabotulinum toxin injections with very different underlying pathologies such as spina bifida in 18 children, acquired spinal cord injury, cerebral palsy, transverse myelitis, intraspinal lipoma, and acquired bladder dysfunction after pelvic surgery or brain injury. Twenty-two of the included children suffered from NDO. All except one child with NDO were on regular CIC. Prior to BTA injection, all children with DO had received anticholinergics and urotherapy. A total of 106 intravesical, 23 intrasphincteric, and five combined injections were analyzed. The dose for intravesical injections was 10 units/kg (maximum: 300 units). The overall median response time was 7 months. BTA remained effective after up to 11 injections. In NDO, the response after each injection was in the >90% symptom reduction category, according to the standardization of terminology suggested by Nevéus et al.[29] In the NDO subgroup, the median response time after BTA injections remained stable up to the 7th injection. The following side effects were

observed: urinary retention in the only child of the NDO subgroup who was not performing CIC, and symptomatic culture positive UTI after 13 of the 134 BTA injections during the first 2 weeks following treatment.

In 2018, a study about 19 children (AA: 10.3±3.1 years) with refractory NDO due to myelodysplasia was published.[41] Botox was injected up to five times (dosage: 10 U/kg; maximum: 200 U). In two patients, macroscopic hematuria occurred, and no other side effects were noted. Clinical and urodynamic parameters improved: All children became completely dry. The median continence duration after repeated injections was between 8 and 10 months. The compliance and MCC increased, and the MDP decreased and remained similar after repeated injections.

The next multicenter study, published in 2018, investigated 53 patients retrospectively (AA: 8.5 years, range 1-15) with neurogenic bladder due to open and closed spinal dysraphism.[42] Up to eight injections were performed. Except for UTI, no complications were found. The clinical success rate was 66%. It increased significantly with a higher maximum urethral closure pressure. The average time interval between injections showed a decrease after the 4th injection. The MCC was significantly improved in patients with DO, but not in patients with isolated low-compliance bladder. Also, the compliance of the bladder did not significantly improve in patients with isolated low-compliance bladder. The MDP was not significantly reduced in all subgroups. Significant urodynamic improvements were found in the subgroup of patients with normal compliance and DO and in the subgroup with poor compliance bladder and DO, whereas patients with poor compliance bladder without DO showed no significant urodynamic improvements. Considering the young age of the patients and the relatively short response time of the injected BTA, alternatives to that treatment without the need of general anesthesia would be very helpful.

Besides the well-known injections of the toxin into the detrusor muscle, electromotive drug administration (EMDA) is used in some more recent studies as an alternative to apply the toxin. EMDA is based on the combination of iontophoresis, electrophoresis, and electroporation. By using an electrical current created between two electrodes, drugs are delivered into deeper tissue layers.[43] Lidocaine and epinephrine are used for local anesthesia during the EMDA procedure. Several experimental[44] and clinical studies[45-47] showed promising results.

In an experimental study,[44] the depth and pattern of BTA distribution throughout the rabbit bladder wall by using intravesical EMDA in comparison to injections was examined. In the BTA/EMDA group, a uniform straining was shown in the urothelium, and interstitial and muscular layers. In the other group, the pattern of immunohistochemical staining was weak and heterogenous.

The first report of intravesical electromotive BTA administration in children with MMC and refractory NDO was published in 2011.[45] In 15 children (AA: 7.8 years), BTA in a dosage of 10 IU/kg was used. Evaluation was performed before and at 1, 4, and 9 months after treatment. An improvement of the urodynamic parameters, and urinary and fecal incontinence and VUR was observed. MBC increased significantly from 121 to 262 mL. The average MDP significantly decreased from 75 cm $H_2O$ to 39 cm $H_2O$. Urinary incontinence improved in 80% of cases. The VUR grade decreased significantly in seven of the 12 children (average VUR grade: 2.25 versus 1.37). Fecal incontinence was alleviated in 83%. The following side effects were observed in six children: skin erythema and a burning sensation.

In another prospective study published in 2016[46] including 16 children (4 –16 years old), the effects of intravesical electromotive BTA administration for the management of concomitant neuropathic bowel and bladder dysfunction were examined. All children had NDO with moderate to severe UI, refractory to conventional treatment and had to use CIC. In addition, the children suffered from bowel dysfunctions such as constipation, soiling, encopresis. BTA (Dysport, Ipsen) was used at a dose of 10 IU/kg. The study showed not only a positive effect on bladder dysfunctions like a significant decrease in the UI score.

In addition, the bowel dysfunction was treated: Constipation symptoms improved in 10 out of 13 of children after 1 year, soiling/encopresis improved in 1 out of 3 children after 1 year, and the average frequency of defecation increased significantly.

BTA is known to modulate both the motor and the sensory neuronal pathways. The underlying mechanisms are not totally understood. The effects of BTA applied by EMDA on bowel dysfunction may have several explanations, such as shared innervations or absorption of toxin by adjacent structures. Also, in this field, more studies are necessary to clarify the underlying mechanisms.

In a long-term follow-up study published in 2017[47] incontinent children with DO due to MMC were treated by intravesical electromotive BTA administration. Twenty-four children (AA: 9±3.6 years, range: 3–16 years) were observed for 6 years. BTA (Dysport) at a dose of 10 IU/kg was used. VUR was observed in 42% of the patients. After 6 months, 88% of the patients became completely dry between CICs. After 1, 2, 3, 5, and 6 years, 75%, 45.5%, 37.5%, 33%, and 29.1% remained completely dry without any additional treatment with BTA. The patients who dropped out were re-treated once, twice, or three times. The average MDP was decreased significantly. During the follow-up, the MCC increased significantly from 148 ml before the treatment to 239, 249, 286, 313, 341, and 356 ml, respectively. VUR was resolved in eight out of 10 children in a 1-year follow-up.

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Constipation that was found in 13 of 24 children before treatment improved in 11 of them after the 1st year.

Further advantages of the EMDA method could be the avoidance of general anesthesia and hereby the avoidance of anesthesia-related risks and complications in younger children, as well as the reduction of costs and the possibility to perform the treatment on an outpatient basis. However, more comprehensive studies in this field are necessary, as well as in the research field about the usefulness of urinary cytokines in the planning for BTA treatment.[48-50]

In conclusion, BTA is a clinically and urodynamically effective and safe treatment for NDO in children. Patients with fibrotic, acontractile bladders with poor bladder compliance (without DO) and children with a very small initial bladder capacity seemed to respond poorly or not at all to BTA treatment. In addition, the presence of an OBN was shown to be an independent predictor of a poor response after the BTA injection. A combined injection of BTA into the detrusor muscle and into the external urethral sphincter may improve the clinical outcome, when detrusor-sphincter-dyssynergia is present. Several studies suggest that in case of a VUR presence, a combination of intradetrusor BTA injections with an endoscopic treatment of the VUR by submucosal injection of a bulking agent are utilized. However, further studies are necessary to prove a potential benefit of this combination therapy. EMDA may be an alternative application method for BTA instead of injections without the need for general anesthesia. However, further research in this field is required. The application method, the minimal clinical effective dosage, inclusion criteria, and prognostic factors for repetitive injections remain to be established in further experimental and clinical prospective studies with a higher number of patients.

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