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Botulinum Toxin A Treatment Into Gastrocnemius In Children With Spasticity – A Follow-up Study

Version 2

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Abstract

Introduction

Cerebral palsy (CP) is the most common motor disability of childhood, with spasticity as the dominating symptom. CP affects boys more often. Spasticity leads to primary problems (pain, loss of motor control), and secondary problems (fixed contractures, limb deformites). Treatment of primary problems may delay development of secondary problems, and thereby surgery. Spasticity can be treated with botulinum toxin A (BTX-A) injections.

Aim

The overall aim of the study was to do a follow-up of children receiving BTX-A injections due to spasticity of the gastrocnemius muscle, during the period January 1998 to December 2015 at the University Hospital in Örebro (USÖ).

Methods

Patient data were collected retrospectively from medical records of the Department of Child and Youth Habilitation, Region Örebro County.

Results

The study comprise 98 patients and 68% were boys. A higher frequency of the boys got their first BTX-A injection at younger age compared to girls. Diplegia was the most common subdiagnose of CP receiveing BTX-A treatment, and most childen had a Gross Motor Function Classification System (GMFCS) level of 1-3. The patients were divided into two groups, group A (n=48, BTX-A treatment during 1998-2006) and group B (n=49, treatment during 2007-2015), and showed a bigger portion of boys in group B than group A. Mean age for both first BTX-A injection and surgery were lower in group B.

Conclusion

In the present study, there was a overweight of boys that received BTX-A injections due to spasticity. Although, the results have to be interpreted carefully, since the prevalence of boys with CP are higher. Nevertheless, it is important to be aware of this possible connection. Diplegia was the most common CP subtype, and most children had a GMFCS level of 1-3.

Abbreviations

BTX-A	Botulinum toxin A
CP	Cerebral palsy
CPUP	Uppföljningsprogram för Cerebral Pares
GMFCS	Gross Motor Function Classification System
MAS	Modified Ashworth Scale

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Introduction

Cerebral palsy is the most common motor disability of childhood, with a prevalence of 1,5-3 per 1000 live births [1-3]. In two Swedish studies, the prevalence for CP was 2,2 respectively 2,7 per 1000 children, and 60% respectively 58% of the children were boys [4,5]. There are different types of CP, of which the spastic one is the most common type, accounting for 60-80% [2,6,7]. Spasticity is associated with primary problems such as pain and loss of strength, balance and motor control, as well as secondary problems, such as fixed contractures and limb deformities [3,6,8-13].

Gross Motor Function Classification System (GMFCS) is a classification system used to classify the degree of motoric disability, based on self-initiated movement, in children with CP. There are five levels of GMFCS. GMFCS level 1-3 means that the child is able to walk by itself with or without aids. GMFCS level 4-5 means that the child's mobility is limited or they are not able to walk [9,14,15]. To estimate spasticity Modified Ashworth Scale (MAS) is used[15,16].

The aims when treating spasticity are to reduce muscle tone, increase range of motion and facilitate muscle stretching to improve function, as well as delaying the need for surgery [9,17]. There are different strategies to achieve these aims, including physiotherapy, orthoses, casting and oral anti-spastic drugs, which are the base treatment for spasticity [12]. Intrathecal baclofen, selective dorsal rhizotomy and neuromuscular blockade are treatment options for primary problems associated with spasticity for selected patients[18]. When secondary problems develop, orthopaedic corrective surgery is often needed to improve muscle balance and thereby function [8,12,19].

By delaying development of secondary problems due to spasticity, the need for surgery could be postponed, or even obviated. The younger the child is by the time for surgery, the more unpredictable are the results for motoric development, and there is a risk that the child needs repeated operations[9,12,18,20,21].

Botulinum toxin type A (BTX-A), a neurotoxin, causes a local reversible paralysis of muscles, by blocking the release of acetylcholine at the neuromuscular junction. The reversibility is due to nerve sprouting that results in restorage of the neuromuscular junction. The effect of BTX-A often varies between 3-6 months[3,7,12,22-24]. BTX-A injections

reduce spasticity of the musculature, and may also lead to pain relief and improved function [11,21]. The indication for BTX-A injections varies among children, depending on severity and distribution of the neurological impairment [25]. Dose recommendations varies due to which muscle is injected, with a maximal dose of 12 U/kg, in total 300 U, at each injection date [2,9].

Serious side effects after BTX-A injections are uncommon, and only reported in 1-2% of the cases. Although, local side effects, such as swelling, bruising and pain, are frequent after injections of BTX-A[25].

Aim

The overall aim of the study was to do a follow-up of children receiving BTX-A injections due to spasticity of the gastrocnemius muscle, during the period January 1998 to December 2015. Questions to be answered were:

1. The biometric data of the study population (gender, CP-type, GMFCS, secondary diagnoses, age at first BTX-A injection).
2. The goal of BTX-A treatment and the effect of BTX-A, both in an objective and subjective view.
3. Side effects after BTX-A injections.
4. Other possible muscles injected in the lower extremities combined with gastrocnemius.
5. Number of patients that underwent surgery (Achilles tendon lengthening or gastrocnemius release) due to equinus feet, and at which age the operation was done.

Material and methods

Data collection

This study is retrospective, descriptive, longitudinal and population based. The patient data were collected from medical records of the Department of Child and Youth Habilitation, Region Örebro County. The study protocol included patient characteristics (sex, age), reason to spasticity treatment, GMFCS level, concomitant diseases, which muscle/muscles that was injected with BTX-A and side effects due to BTX-A treatment. Age at first BTX-A injection was summarized. If the patient underwent surgery because of equinus feet, data about age at operation and type of operation were collected. To compare spasticity before and after BTX-A, MAS were collected, and also information about patients and/or parents experiences of the

effect of BTX-A. No scale system was used measure pain, why the information was difficult to obtain.

Participants

The study group comprise children (<18 years) registered at the from Department of Child and Youth Habilitation in Region Örebro County who had received BTX-A injections into gastrocnemius, in some cases combined with injections into other muscle group too, at University Hospital Örebro (USÖ), during the period January 1998 to December 2015. Children who got BTX-A injections into other muscles, without combination with gastrocnemius, were excluded.

Statistical analysis

The software used for statistical analyses was SPSS, version 23. The different variables were analysed with Pearson Chi-Square test. A p-value lower 0.05 was considered as statistically significant.

Ethics

The study did not result in any extra BTX-A injections or medical care for the patients. The person in charge of the Department of Child and Youth Habilitation approved that medical records of the patients concerned were reviewed. Data that could reveal the identity of the patient is not published, and the patient's identity is therefore anonymous.

Results

In total, 125 children got BTX-A injections into muscles in the lower extremity. Two of these children were not found in the medical records, and were therefore drop-outs. Twenty-five of the children received BTX-A into other muscles, without combination with gastrocnemius (hamstrings, adductors, iliopsoas, tibialis posterior), and were excluded from this study. 98 children were included in the study (95 with CP) *(figure 1)*.

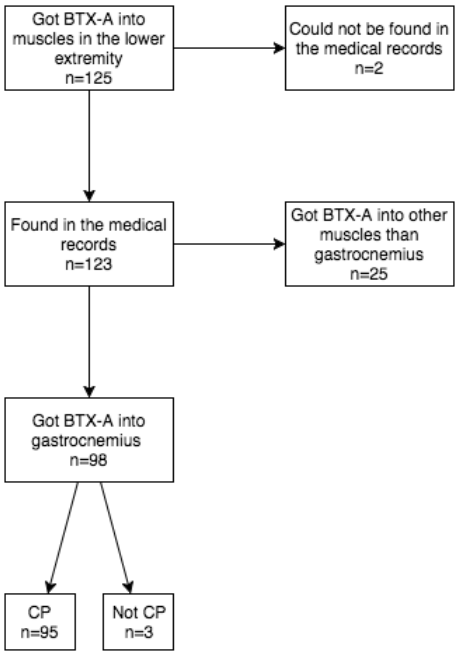

Figure 1 Flow chart of study participant selection.

Gender

Two thirds of the 98 patients were boys. When the normal distribution of CP between genders was set to 50:50, statistical significance was found ($p<0.001$), but since CP is more common in boys, the distribution between genders in the present study was compared with two Swedish studies[4,5]. Statistical significance was found when the normal distribution of CP between boys and girls was set to 58:42 ($p=0.038$), but not when it was set to 60:40 ($p=0.091$). In the GMFCS level 1-3 group the distribution among boys (67%) and girls were more similar, while there was a bigger difference in gender distribution in the GMFCS level 4-5 group (boys 77%) (*figure 2*).

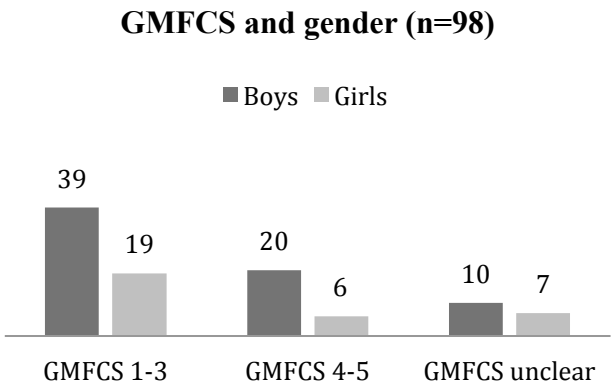

Figure 2 Distribution in GMFCS level and gender in children with CP,

Diagnoses

Almost (97%) of the patients had CP, whereof the most common types were spastic diplegia (56%) and spastic hemiplegia (28%). Fifty-nine percent of the patients had GMFCS level 1-3,

and 27% had GMFCS level 4-5. For 14% of the CP children the GMFCS level were not documented in the medical records. Of the three remaining patients, that did not have CP, two patients had acquired brain injuries and one patient had aqueductal stenosis, which caused spasticity.

Twenty-eight percent of the children did not have any other diagnoses than CP, while the remaining had secondary diagnoses. The most common secondary diagnoses were mental retardation (39%), epilepsy (30%) and visual impairment (27%). Of the children in GMFCS level 1-3-group, 62% had at least one secondary diagnose. The corresponding number in the GMFCS level 4-5 group was 89%. Secondary diagnoses were about equally common between the genders.

Indications

Most of the patients had multiple indications for BTX-A treatment, whereof the most common indication (59%) was to improve motor activity (walking, standing, balance).

GMFCS

In the GMFCS level 1-3 group, 50% of the children achieved BTX-A injections into several muscles, while the corresponding number of patients who got injections into several muscles in the GMFCS level group 4-5, was 85%.

Age

Five patients got BTX-A injections at other hospitals before treatment at USÖ, and for one patient data for the first injection were missing. The mean age for injection start for the remaining 92 children were 6,0 years (1,8 years-16,8 years). The patients were divided into two groups, based on the first BTX-A injection. Medical records regarding first injection were missing for four patients. For the remaining 94 children, a bigger part of boys got their first BTX-A injection at younger age than girls did. Also, a bigger part of girls got their first injection when they were older than nine years *(figure 3)*.

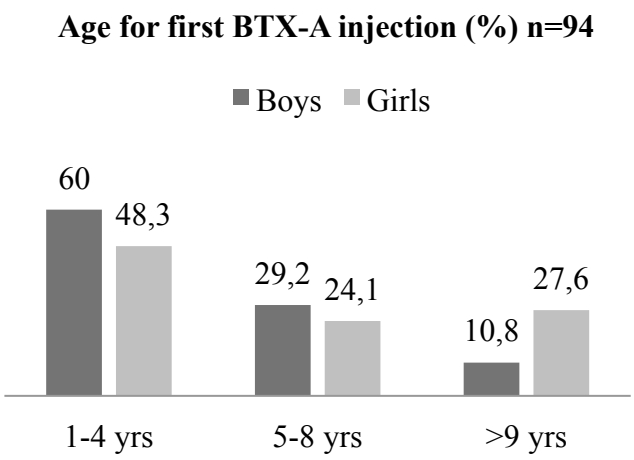

Figure 3 Age for first BTX-A injection.

Side effects

Fourteen percent of the patients got side effects because of BTX-A treatment. The distribution of side effects is shown in *table 1*.

Table 1 Distribution of side effects post-BTX injection.

Side effects	Number of children
Weakness	5
Pain post-BTX	4
Impaired balance	2
Increased tension	1
Fever	1
Urinary incontinence	1
Increased salive production	1
Itch	1

Effect of BTX-A

For 62% of the children, there was a decrease in the Modified Ashworth Scale (MAS) one to three months after BTX-A injection, at least at one point of time post-BTX. When the effect of BTX-A terminated, MAS returned to the same level as before BTX-A injections were given. Nineteen percent of the children did not achieve any decrease in MAS post-BTX-A, and for 18% of the children data about MAS before and/or after BTX-A injections were missing. In a subjective view, 69% of the children and/or the parents experienced that BTX-A had a positive effect in reducing spasticity. Eleven percent did not experience any effect, and for 19% data about the subjective experience was not documented in the patient's medical record. Twenty-seven percent of the patient's had notes about their pain situation pre-BTX-A, and if BTX-A had any effect regarding the pain. For the remaining patients, no notes about pain were found in the medical records.

Surgery

Thirty-nine percent patients underwent surgery because of equinus feet (Achilles tendon lengthening or gastrocnemius release). Five of these patients underwent surgery before they got their first BTX-A injection, and 5 patients underwent surgery during the same period as they got BTX-A injections. The mean age for surgery were 8,4 years, but if the five patients that were operated before their first BTX-A injection are excluded, the mean age were 9 years. The most common age interval for surgery were 5-11 years (73%). 11% of the children who underwent surgery did that before the age of 4 years, and 3% underwent surgery at an age over 17 years.

Follow-up over time (two groups)

The patients were divided into two groups, one group including children who begun BTX-A treatment during 1998-2006 (group A, n=48), and one group including children who begun treatment during 2007-2015 (group B, n=49). In group A, 63% had diplegia and 19% hemiplegia, while the corresponding number of children in group B was 49% respectively 35%. The number of children with other types of CP (tetraplegia, dyskinesia, ataxia) were almost the same for the different groups. In group B the GMFCS level was unclear only for some few children *(figure 4)*. In group A, 63% of the children were boys and in group B, 74% were boys.

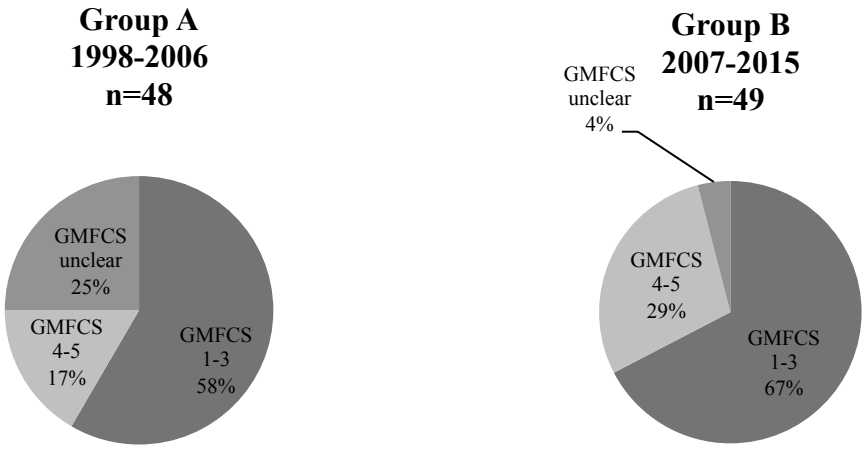

Figure 4 GMFCS-levels for the patients who started with BTX-A injections (into gastrocnemius, in some cases combined with other muscle groups in the lower extremity) under the period 1998-2007 respectively 2008-2015.

The relationship between gender and a low GMFCS level in respectively group was almost similar *(table 2)*.

Table 2 Gender (%) with a low GMFCS level (1-3) in group A (1998-2006) and B (2007-2015).

Period	Boys (%)	Girls (%)	Total (%)
1998-2006	39,6	18,8	58,4
2007-2015	46,9	20,4	67,3

Mean age for first injection of BTX-A were 6,6 years in group A. In group B, mean age at first injection were 5,4 years. Patients that had their first BTX-A injection at other hospitals than USÖ was not included (5 patients, all of them belonging to group B), neither was the patient who missed data about when the first injection were given (also belonging to group B). Mean age at surgery was 9,8 in group A, and 8,0 years in group B (excluding the five patients who underwent surgery before they got their first BTX-A injection). There were two different methods used for surgery of equinus feet during the actual period – Achilles tendon lengthening respectively gastrocnemius release. In group A, 30% of the children underwent gastrocnemius slides, while the corresponding number in group B was 38%,

Except the differences in gender, no results were statistically significant (p-value lower than 0,05).

Discussion

It was not possible to find the distribution of CP among genders in Örebro County during the actual study period. Of the children who got BTX-A injections into gastrocnemius, 68% was boys, which is statistically significant compared to the expected distribution in the population[4]. Since the gender distribution varies between different studies, statistical significance was not found when the results of the present study were compared with another study [5]. The study by Himmelmann et [5]al do not mention at which age the children were examined, but focus more on birth characteristics and the aetiology of CP, while the study by Westbom[4] et al examine children with CP with an age of 4-11 years. In the present study, mean age for first BTX-A injection was 6,0 years, and therefore the study by Westbom et al may be more suitable for comparison with the present study. Nevertheless, it is important to be aware of this possible connection regarding differences between gender.

The reason why boys might receive BTX-A injections more often is unclear. One hypothesis could be that boys are more motoric active than girls. Because spasticity is velocity-dependent [2], the higher motoric activity in boys may explain why BTX-A injections were more

common for them. The fact that it was more common for boys to start with BTX-A injections at an age of 1-4 years, than it was for girls to start treatment at that age, may also depend on higher motoric activity in boys compared to girls.

Secondary diagnoses were more common in children with GMFCS level 4-5, as well as the frequency of injections into other muscles combined with gastrocnemius. Children with GMFCS level 4-5 are more disabled than children with a lower GMFCS level [14], and a higher GMFCS level is associated with more widespread problems with spasticity [26]. This could explain why BTX-A treatment into other muscles than gastrocnemius was more common in children with a higher GMFCS level.

It was more common that children with GMFCS level 1-3 had BTX-A treatment, and they are also able to walk, which could explain that the most common indication for BTX-A was ”to improve motor activity”.

Fourteen percent of the children got side effects due to BTX-A treatment. The frequency of side effects was expected to be lower, given to the available literature[25,27]. Although, some of the side effects may not actually be side effects but only a coincidence (for example fever). The most common side effect in this study was weakness. The goal with BTX-A treatment is to reduce spasticity, and thereby weaken the muscle. This may lead to consideration about if weakness really is a side effect due to BTX-A injections. Although, in another study [28], weakness was considered as a side effect due to BTX-A injections, why we followed the example of that study. Anyhow, if weakness had not been considered as a side effect, the prevalence of side effects in the present study would have been lower (9%).

It was more common that children and/or parents experienced a subjective effect on spasticity after BTX-A treatment, compared to MAS. This indicates the importance to also evaluate the children’s and/or parents’ own experience of BTX-A treatment, since functional improvements also influence the daily living.

Only 27% of the children had notes about their pain situation in their medical records. Pain is a well-known problem following spasticity [13], and discussions about pain situation were expected to be commonly occurring in the medical records. Maybe the pain situation had been

discussed for more patients than 27%, but if so, it was not mentioned in the child's medical records.

Over time, age for BTX-A treatment has decreased, as well as age for surgery, which is a bit surprising, since BTX-A injections are supposed to delay the time for surgery [9,12]. There was a lower age for treatment and a bigger portion of children with a low GMFCS level in group B, that could explain the earlier need of spasticity reduction, since they are walking. In 2007 the Department of Child and Youth Habilitation in Örebro County joined a national quality register (CPUP, Uppföljningsprogram för Cerebral Pares), which among other parameters evaluates the children's GMFCS level [15]. The introduction of CPUP may explain the bigger part of unknown GMFCS levels in group A, compared with group B.

There were also differences regarding to the diagnoses in the two different groups. Diplegia was the most common CP-type in both groups, but there were a higher percentage of children with hemiplegia in group B compared with group A. A Swedish study states that hemiplegia has increased since 1990s, which could also be seen in the present study [5]. Fazzi et al found that children with hemiplegia benefits more from BTX-A treatment, and also that the effect of BTX-A is better the younger child [29]. On the other hand, age for surgery was also lower in group B. One hypothesis could be a shorter waiting time for surgery. Also, the indication for surgery is a subjective assessment, and maybe there was different surgeons assessing most of the patients in group A respectively B. The lower age in group B could not be explained by differences in operation method, because the distribution between the two different operation methods were almost alike in the different groups.

The reason why the children were divided into two groups was based on the point of time for their first BTX-A injection, and not divided in to groups based on during which point of time they were under BTX-A treatment, was because some children were under treatment during both the time periods (1998-2006 and 2007-2015). Therefore, it was impossible to divide the children based on the time they were under BTX-A treatment. Anyways, if it would have been possible to diviede the patient's into two groups in that way, the results could have been different.

Limitations

The greatest limitation of this study is the lack of a control group, consisting of children with spasticity that was not receiving with BTX-A injections. One idea was to create a control group consisting of children with spasticity during a period before BTX-A injections were introduced in Örebro County, but there was a problem to bring out these children's medical records. Another way to create a control group would have been to recruit children belonging to other hospitals, where BTX-A injections have not yet been introduced. To create a control group when BTX-A injections already were introduced, would not have been ethically correct, because BTX-A injections is showed to reduce spasticity [2], and equal care would not have been performed if some patient, who could be helped by BTX-A injections, would be denied this intervention.

Another limitation is that some children's medical records did not cover all the parameters reviewed in this study. For example, some medical records missed data about GMFCS level, and these children were excluded when compiling GMFCS level for the whole group of children. The same thing applies to age for first injection, MAS and objective effect of BTX-A injections.

For further research to be done, a standardised protocol is desirable. The protocol could then be used for all patient's receiving BTX-A injections, when treatment results are followed up. Except GMFCS-level, MAS and subjective effect of BTX-A injections, a suggested parameter to evaluate is pain. The use of such a protocol allows a prospective follow-up to be done.

Strengths

Strengths of this study are the relatively big study population and the long period of time the participants, at least the patients who begun BTX-A treatment in the beginning of the studied period, have been followed up.

Conclusions

Under the period 1998-2015 it was more common for boys to receive BTX-A injections, and a bigger portion of boys started with BTX-A injections in a younger age. In the patient's medical records, discussions about pain situation occurred rarely. Over time, age for beginning with BTX-A injections have decreased, as well as age for surgery due to spasticity

in gastrocnemius. Further research is needed in the future to evaluate the long-term effects of BTX-A treatment that also includes functional improvements in daily life.

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Populärvetenskaplig sammanfattning

Cerebral pares (CP) är en vanlig orsak till rörelsehinder hos barn, och drabbar något fler pojkar än flickor. CP orsakar ofta spasticitet, som i sin tur kan leda till smärta och svårigheter med rörelse och balans. Spasticitet kan behandlas med botulinumtoxininjektioner i den aktuella muskeln. Botulinumtoxin är ett nervgift som gör att muskeln slappnar av, vilket leder till förbättrad rörelse och balans, mindre smärta och senareläggande av eventuellt behov av operation.

Syftet med denna studie var att göra en uppföljning av de barn som behandlats med botulinumtoxin i vadmuskulaturen, under perioden januari 1998-december 2015, på Universitetssjukhuset i Örebro.

Totalt behandlades 98 barn, varav drygt 2/3 var pojkar. Det var en större andel pojkar som började behandlas med botulinumtoxin i en yngre ålder än flickor. Orsaken till olikheterna mellan könen avseende behandling med botulinumtoxin är oklar, men att det fanns en skillnad mellan könen är uppenbart. Kanske är det en slump att skillnader mellan könen sågs. En hypotes kan annars vara att pojkar är mer motoriskt aktiva än flickor, och eftersom spasticitet är hastighetsberoende, blir spasticiteten mer märkbar hos pojkar. I studien framkom det också att åldern för första botulinumtoxininjektion med tiden har minskat, likasom ålder för operation på grund av spasticitet.

Cover letter

December 8th, 2016. Corresponding author: Sofia Magnusdotter, Bachelor of Medicine, Örebro University

Botulinum Toxin A Treatment Into Gastrocnemius In Children – A Follow-up Study

Dear Editor

In this longitudinal study, a follow-up of children who received botulinum toxin A (BTX-A) injections into gastrocnemius because of spasticity, were done. During the follow-up period (January 1998 to December 2015) 98 children received injections. The most interesting finding was the differences between genders. More boys received BTX-A injections, and there was a bigger part of boys who received their first injection in a younger age compared to girls. What we know, no other studies with such findings have been published before, and therefore this study comes with new facts about gender differences in health care, an up-to-the-minute topic in this time.

Has not been published before and is not considered for publication elsewhere.

Best regards

Sofia Magnusdotter

Ethical considerations

This is a longitude study that examines clinical treatment, with the aim to do a follow-up of the children who received BTX-A injections into gastrocnemius in Örebro County. Studies with the aim to examine clinical treatment are an important part of research, because it helps the caregivers to understand what is good and what could be improved in daily health care. Therefore, such studies could help to improve health care, and thereby treatment results and patient security.

The children in this study were not exposed to any extra BTX-A injections or other interventions in health care, because the present study's design was retrospective. When the children's medical records were reviewed, replacing the personal identity number with a study code impersonalised every child. No data that could be linked to the patients are published in the study.

Because of this study is not supposed to be published, but is only a study which examine clinical treatment for a patient group registered at the Department of Child and Youth Habilitation in Örebro, no ethical approval have been asked for from the Ethics Committee. The person in charge for the Department of Child and Youth Habilitation approved that the medical records of the patients concerned were scrutinized.

Although the approval to review medical records concerning children who received BTX-A injection form the person in charge for the Department of Child and Youth Habilitation, it is a student, who has nothing to do with the patient's to do, who has reviewed the medical records. One can wonder whether people who are not a part of the treatment team for each individual child really shall be given access to confidential information about a person's health.