Cost-effectiveness of botulinum neurotoxin A versus surgery for drooling: a randomized clinical trial

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This article is commented on by Shih on page 1234 of this issue.

PUBLICATION DATA
Accepted for publication 8th June 2020.
Published online 24th July 2020.

ABBREVIATIONS

ICER	Incremental cost-effectiveness ratio
RCT	Randomized controlled trial

AIM This study compared the cost-effectiveness of botulinum neurotoxin A (BoNT-A) injections with two-duct ligation of the submandibular glands as treatment for severe drooling after one treatment cycle.
METHOD The study was part of a larger, partly single-blinded, randomized clinical trial (trialregister.nl identifier NTR3537). Data were collected between 2012 and 2017. Evaluation was at 32 weeks after one treatment cycle. Fifty-seven patients with cerebral palsy or other neurological, non-progressive disorders and severe drooling classified as having a drooling frequency ≥3 or a drooling severity ≥2, in whom conservative treatment was deemed ineffective, were randomized to treatment by BoNT-A or two-duct ligation. An incremental cost-effectiveness ratio (ICER) was calculated using the success rates as the measure of benefit. Treatment success was defined as a decrease ≥50% from baseline to 32 weeks in the subjective visual analogue scale for the severity of drooling or the objective drooling quotient.
RESULTS Fifty-three patients were analysed (22 females, 31 males; mean age 11y, range 8–22y). Average costs for one treatment cycle, which included one BoNT-A injection, were €1929 (standard error 62) for BoNT-A and €3155 (standard error 99) for two-duct ligation. Treatment success was in favour of two-duct ligation (63% vs 27%; number needed to treat 3). The ICER was €34 per 1% gain in treatment success in favour of two-duct ligation versus BoNT-A.
INTERPRETATION The additional cost of two-duct ligation is to some extent offset by a larger treatment success rate compared with BoNT-A.

Drooling is a well-known problem in children with neurodevelopmental disabilities. It can cause physical and psychosocial problems for the patient as well as damage personal belongings.[1–3] It is detrimental to quality of life and is associated with notable health care costs.[4]

Currently, when conservative treatment (speech and language therapy or behavioural therapy) has failed, intraglandular injection of botulinum neurotoxin A (BoNT-A) is the treatment of first choice. The procedure is effective in 46.6% of children. Side effects occur in 33% of patients, but these are usually mild and subside within a few weeks. The effect of BoNT-A injections is always temporary and lasts for a median of 22 weeks.[5–7]

Over the past two decades, ligations of the submandibular and/or parotid ducts have gained popularity. These procedures are attractive as they are technically straightforward, require little operative time, and can take place in a day-case setting.[8,9] Compared with submandibular gland excision or duct re-routing, duct ligation is associated with less postoperative morbidity.[6] More specifically, recent literature has reported that two-duct ligation was effective in more than 60% of patients after 32 weeks, and there were limited complaints and risks of serious adverse events related to the procedure (4%).[9–12]

Analyses of cost-effectiveness are becoming increasingly popular as instruments to facilitate health care decision-making. The cost-effectiveness of a health care intervention is determined by opportunity cost and benefit gains. The costs and cost-related effectiveness of the different treatments for drooling are currently unknown. This study aimed to compare the cost-effectiveness of BoNT-A treatments with the two-duct ligation intervention for the treatment of drooling in patients with neurodisabilities after one treatment cycle of 32 weeks.

METHOD

This, partly single-blinded, analysis of cost-effectiveness was part of a randomized controlled trial (RCT) conducted

 DOI: 10.1111/dmcn.14636

between April 2012 and August 2017 approved by an independent regional ethics committee (Commissie Mensgebonden Onderzoek regio Arnhem – Nijmegen). A detailed report of the trial and study design, participants, intervention protocols, and masking was previously published.[10] Partly single-blinded meant that we blinded researchers to the objective outcome but not to the subjective outcome.

This RCT was approved by an independent regional ethics committee (Commissie Mensgebonden Onderzoek regio Arnhem – Nijmegen) and was registered in the Dutch Trial Register (trialregister.nl identifier NTR3537). Written informed consent was received from all caregivers of the patients in the study.

Participants

Inclusion criteria were a diagnosis of cerebral palsy or other neurological non-progressive disorder, an age of 8 years or older, and severe drooling which was qualified as a drooling frequency ≥3 or a drooling severity ≥2. Drooling severity scores were: 1, none; 2, mild; 3, moderate; 4, severe; 5, profuse; drooling frequency scores were: 1, never; 2, occasional; 3, frequent; 4, constant.[13]

For all participants, oral therapy did not offer satisfactory results or was judged to be ineffective on the basis of the intellectual capacity or physical status of the patient. Patients were excluded from participating if they had undergone previous surgery or had anatomic head or neck anomalies interfering with either treatment. Additional exclusion criteria were simultaneous treatment for drooling or suspected progressive oromotor impairment.

Study participants were randomized to either two-duct ligation or a single injection with onabotulinum toxin A (25 units in 0.9% saline per submandibular salivary gland; Botox; Allergan; Nieuwegein, the Netherlands). All procedures were conducted in an outpatient setting at the Radboud University Medical Center, Nijmegen. The detailed protocols for these procedures have been reported in a previous publication by the same research group.[10]

There was concealment of allocation from those assigning patients to either BoNT-A or two-duct ligation, until the moment of assignment. All patients were randomized in a 1:1 ratio using an electronic randomizing program. Patients were stratified on the basis of sex, age, presence of cerebral palsy, and Gross Motor Function Classification System (GMFCS) level.

Blinding of researchers and hospital staff was not possible owing to the visible difference between the two interventions; therefore, drooling quotient measurements were recorded for subsequent evaluation by a speech and language therapist blinded to treatment allocation.

All patients participating in the trial visited our outpatient clinic for measurements at baseline, and at 8 and 32 weeks post-intervention. Patients were evaluated by a speech and language therapist and an ear, nose, and throat consultant at baseline. Measurements at baseline, and at 8 and 32 weeks, were primarily performed by the dedicated speech and language therapist. Two-duct ligation was performed by an ear, nose, and throat consultant and BoNT-A injection was performed by a rehabilitation consultant. According to the trial design, a telephone consultation with an ear, nose, and throat consultant was scheduled after a procedure to assess complaints or complications 1 week postoperatively.

What this paper adds

- Botulinum neurotoxin A (BoNT-A) is less expensive per percentage of success than two-duct ligation.
- The additional cost of two-duct ligation over BoNT-A is offset by greater treatment success.

Primary outcomes

The incremental cost-effectiveness ratio (ICER) was calculated using the success proportions as the measure of benefit. This was calculated using the mean total cost and the treatment success defined as either a reduction ≥50% in drooling quotient or visual analogue scale for the severity of drooling after 32 weeks. This definition is now the standard to determine treatment success in our institution.[10–12,14] All baseline and follow-up measurements consisted of an assessment of the drooling quotient and visual analogue scale for severity of drooling. The drooling quotient is a validated direct-observational semi-quantitative method to assess the severity of drooling. New saliva dripping over the lips with intervals of 15 seconds is assessed for 5 minutes, which results in a drooling quotient between 0 and 100%.[15] These observations were performed by specially trained speech therapists. Caregivers were asked to report a visual analogue score, on a scale from 0 to 100, reflecting the severity of drooling over the previous 2 weeks.[10,16] All participants were provided with a cost diary upon inclusion, in which they were asked to note all costs, complaints, and medical encounters (e.g. use of medication, additional visits to general practitioners, or additional hospital visits) in the 2 weeks after an intervention. Patients were asked for complications and external medical encounters 8 and 32 weeks postoperatively. Operation times and internal visits were extracted from hospital records.

In this analysis of cost-effectiveness, we used a societal perspective approach, including all costs associated with the operation, admission, caregiver's loss of productivity, community costs, caregivers' (travel) expenses, as well as costs due to complications and follow-up. An overview of the costs included can be found in Table 1.

Data on health care use were collected from visits to our outpatient clinic, hospital records, and the cost diary. During follow-up measurements, patients were asked whether there had been consultations or admissions outside our clinic, and whether there were any changes in medication. Reference prices for resources from a Dutch guideline on economic analyses in health care were used when applicable.[17,18] If reference prices were unavailable or inaccurate for our analysis, cost price calculations were applied, using a micro-costing approach. Medication costs outside the hospital were estimated using the average price per prescription line or the

Table 1: Overview of costs

Category	Cost (€)
Operation room[a]	Day clinic stay: 294.75[b] Consultant/h: 120.68[b] Operation room team and anaesthetics team/h: 808.72 (880.17)[c] Material two-duct ligation: 97.37[d] Material botulinum neurotoxin A: 185.21[d,e]
Tertiary care[a]	Outpatient clinic: 174.08[b] Hospital stay: 685.62[b] Consult by telephone: consultant: 91.83[b] Consult by telephone: intern: 18.15[b] Outpatient clinic speech therapy/h: 107.96
Medication[a]	First prescription: 12.70 Repeated prescriptions: 6.35[f]
Costs made outside tertiary care[a]	Visit at the general practitioner: 35.24[b] General practitioner consultation by telephone: 18.15[b] General practitioner house call: 53.40[b] Outpatient clinic secondary care: 85.43[b] Hospital stay secondary care: 462.51[b] Psychologist/h: 100.39[b]
Transport (distances and parking tariffs)[g]	Transport costs: 0.20/km Patient's house, apothecary: 0.49km Patient's house, general practitioner: 0.42km Patient's house, secondary care hospital: 2.66km Patient's house, tertiary-care hospital: varied Parking costs at the tertiary-care hospital: 8.47 Parking costs secondary care hospital: 3.18
Absence of work[g]	Adult: average productivity costs/h: 37.11[b] Child: unknown

Reference prices for health care resources from a Dutch guideline on economic analyses in health care were used when applicable.[17,18] Medication costs outside the hospital were estimated by using the average price per prescription line or the price for standard packages in the case of over-the-counter medication (Medicijnkosten.nl). [a]Direct costs, which include costs for outpatient appointments, medication, visits to the general practitioner or local hospitals, the surgical procedure, material, and visits to day clinics. [b]Prices are corrected for the Dutch consumer price index of 2019. [c]Operation room costs without average material costs, original price between brackets. The operation room team consists of three operation room workers and an anaesthesiologist. [d]Including 6% taxes for medical material. [e]Price includes 50IE Botox. [f]Basic apothecary prices per prescription; this price is combined with the price for each prescribed drug (source: www.medicijnkosten.nl). [g]Indirect costs, which include costs incurred by patients or caregivers for transportation, childcare, and sick leave.

price for standard packages in the case of over-the-counter medication.[19] Hours of absence at work reported by parents or caregivers were multiplied with the standard price for average productivity costs per hour for paid workers. For visits to the drooling centre, the average distance to the patients' homes was calculated; for other health care-related transportation, we used standard distances. These distances were multiplied with a standard rate of euros per kilometre. Parking costs were added to every hospital visit. Cost estimates were adjusted for inflation using the annual Dutch consumer price index for 2019. Direct costs included costs for the surgical procedure, material, visits to day clinics, outpatient appointments, medication, and visits to the general practitioner or local hospitals. Indirect costs include costs incurred by patients or caregivers for transportation, childcare, and sick leave. All costs were assigned to three different time intervals. The first interval (T_1) consisted of the preliminary work-up for undergoing the procedure, which included visits to the speech and language therapist, otolaryngologist, and anaesthetic outpatient clinic, and the costs made during the intervention and the medicine that was prescribed per protocol. The second interval (T_2) included additional costs due to complications, such as additional hospital visits, consultations by telephone or medication changes up to 8 weeks postoperatively, and the follow-up visit at 8 weeks. We also added costs for the lost productivity of the parents, as well as costs for additional childcare due to the operation. We used mean imputation in the case of missing cost diaries for loss of productivity and additional childcare. The third interval (T_3) contained any additional health-related costs that occurred between the 8- and 32-week follow-up visit and the 32-week follow-up visit.

Statistical analysis

Cost-effectiveness was calculated using the proportion of success from the RCT. Descriptive statistics were computed for our patients' characteristics, using means and ranges where appropriate. Pearson's χ^2 tests were used to analyse whether there was a significant difference in success between the two treatments and the caregivers'/patients' wishes for follow-up treatment. Confidence intervals (CIs) and number needed to treat were reported when applicable. Number needed to treat indicates the number of patients needed for a specific treatment that results in one additional successful outcome. Student's *t*-tests were applied to evaluate the time spent in the operation room. A generalized linear model was used to predict cost differences between BoNT-A and two-duct ligation. A Kolmogorov–Smirnoff test and *Q–Q* plots were used to analyse potential skewness of the cost distribution. On that basis, a gamma distribution and log link (relating the conditional mean cost to the covariates) was chosen for the generalized linear model. An ICER was calculated using the mean total cost differences and the treatment success after completing the trial. To assess the uncertainty in the ICER and identify the key cost drivers, we performed a sensitivity analysis for the duration of the surgical procedure in intervals of 5 minutes up to a minimum of 41 minutes. The sensitivity analysis included duration of the surgical procedure because the duration of two-duct ligation was dependent on the learning and/or teaching situation in the academic hospital. We did not perform a sensitivity analysis for the loss of caregivers' working hours because this is supposedly a direct effect of the invasiveness of the procedure. When patients crossed over to the other treatment arm, they were analysed according to the

intention-to-treat principle. Patients who were excluded or who withdrew from the study were not included in the analyses.

The power analyses showed that 26 patients per treatment arm were required to provide 80% power with 40% treatment success after BoNT-A and 80% treatment success after two-duct ligation to reveal a difference with a type 1 error rate of 5% wherein a 10% dropout rate was included.[10]

RESULTS

Demographics

Fifty-seven children were randomized to either two-duct ligation or BoNT-A. Four children withdrew from the study or were excluded from analyses. One other child was randomized for two-duct ligation but opted for, and underwent, BoNT-A injections instead. Fifty-three patients (22 females, 31 males; mean age 11y, range 8–22y) were eligible for analysis (BoNT-A 26, two-duct ligation 27). Detailed reasons for exclusion (n=4), including the flow diagram and demographics (Table 2), were reported in a previous paper.[10] Demographics were closely matched and there were no statistically significant differences between the treatment arms at baseline.

Between the two interventions, there was a statistically significant difference in clinical success proportion in favour of two-duct ligation (difference 36.1%, 95% CI 18.1–54.1, number needed to treat 3, 95% CI 2–6, p=0.008). This corresponds to a treatment success of 63% 32 weeks after two-duct ligation and 27% after BoNT-A treatment.

Table 2: Characteristics of study population at baseline

	BoNT-A	Two-duct ligation
Sex, *n* (%)		
Male	15 (57.7)	16 (59.3)
Female	11 (42.3)	11 (40.7)
Age at intervention, mean (range), y:mo	11:2 (8:0–17:9)	11:1 (8:0–22:3)
Diagnosis		
CP	17 (65.4)	14 (51.9)
Non-CP[a]	9 (34.6)	13 (48.1)
GMFCS level (n=31)[b]		
II	2 (11.8)	1 (7.1)
III	3 (17.6)	0
IV	5 (29.4)	8 (57.1)
V	7 (41/2)	5 (35.7)
Degree of mobility[c]		
Ambulant	11 (42.3)	10 (37.0)
Non-ambulant	15 (57.7)	17 (63.0)
Mental ability		
Developmental age <4y	15 (57.7)	15 (55.6)
Developmental age >4y	11 (42.3)	12 (44.4)
Previous BoNT-A injections, mean (SD)	1.62 (1.79)	1.44 (1.25)

Data are *n* (%) unless otherwise stated. [a]Non-cerebral palsy (CP) consists mainly of children with a developmental disorder based on a syndrome, genetics, or metabolic disorder. [b]Gross Motor Function Classification System (GMFCS) level only applies to CP. [c]Based on the GMFCS: patients in levels I–III were graded as ambulatory; patients in levels IV or V were graded as non-ambulatory. BoNT-A, botulinum neurotoxin A.

Figure 1 presents an overview of the average direct (related to and not related to the procedure) and indirect costs and distribution over the three intervals. The costs made over the three intervals in the BoNT-A and the two-duct ligation groups were both significantly atypical. The estimating equations in the generalized linear model showed that the cost ratio of BoNT-A compared with two-duct ligation was 61.1% wherein the average cost per BoNT-A treatment cycle was €1929 (standard error 62) and that for the two-duct ligation group was €3155 (standard error 99).

The ICER was calculated as the incremental costs divided by the incremental effectiveness. The incremental costs were calculated as the difference between the total costs for two-duct ligation and the total costs for BoNT-A. The incremental effectiveness was the difference between the treatment success proportion for two-duct ligation and that for BoNT-A (0.63−0.27=0.36). The ICER was €34.06 per 1% gain of success when using two-duct ligation instead of BoNT-A, which was calculated by dividing the mean total cost difference of €1226 (€3155–€1929) by the difference in treatment success (36%).

Comparison over the three intervals separately showed lower BoNT-A costs in T_1 (BoNT-A: mean €1227, 95% CI 1304–1154; two-duct ligation: mean €1942, 95% CI 2062–1829) and T_2 (BoNT-A: mean €414, 95% CI 489–350; two-duct ligation: mean €941, 95% CI 1109–798) and higher costs in T_3 (mean €288, 95% CI 324–256; two-duct ligation: mean €271, 95% CI 305–242).

Major contributors to the difference in costs were the time spent in the operation room (T_1) and caregivers' loss of working hours (T_2). The average total operation room-time was significantly lower for the BoNT-A group (mean 17min, SD 10.33) than the two-duct ligation group (mean 61min, SD 20.94), resulting in significantly lower BoNT-A operating theatre costs (mean €453) compared with two-duct ligation (mean €1049) (difference −€596, p<0.001, 95% CI −454 to −738).

The sensitivity analysis for the time of the two-duct ligation procedure revealed an ICER of €31.89 per 1% gain of success at a mean surgical duration of 56 minutes, an ICER of €29.75 at 51 minutes, an ICER of €27.59 at 46 minutes, and an ICER of €25.45 at 41 minutes.

We assessed the loss of working hours of the caregivers as well as estimating their contribution to the large difference in costs between the two interventions in T_2. Seventy-four per cent (n=39) of the cost diaries were returned. In the BoNT-A group (n=18), 27.8% reported missing working hours; in the two-duct ligation group (n=21) this was 81.0%. There was a significant difference in loss of production: €99 for BoNT-A and €465 for two-duct ligation (difference −€392, p<0.001, 95% CI −216 to −570). Accordingly, patients treated with BoNT-A missed an average of 1.8 hours of school or work (range 0–8h, standard deviation 2.98), and the patients treated with two-

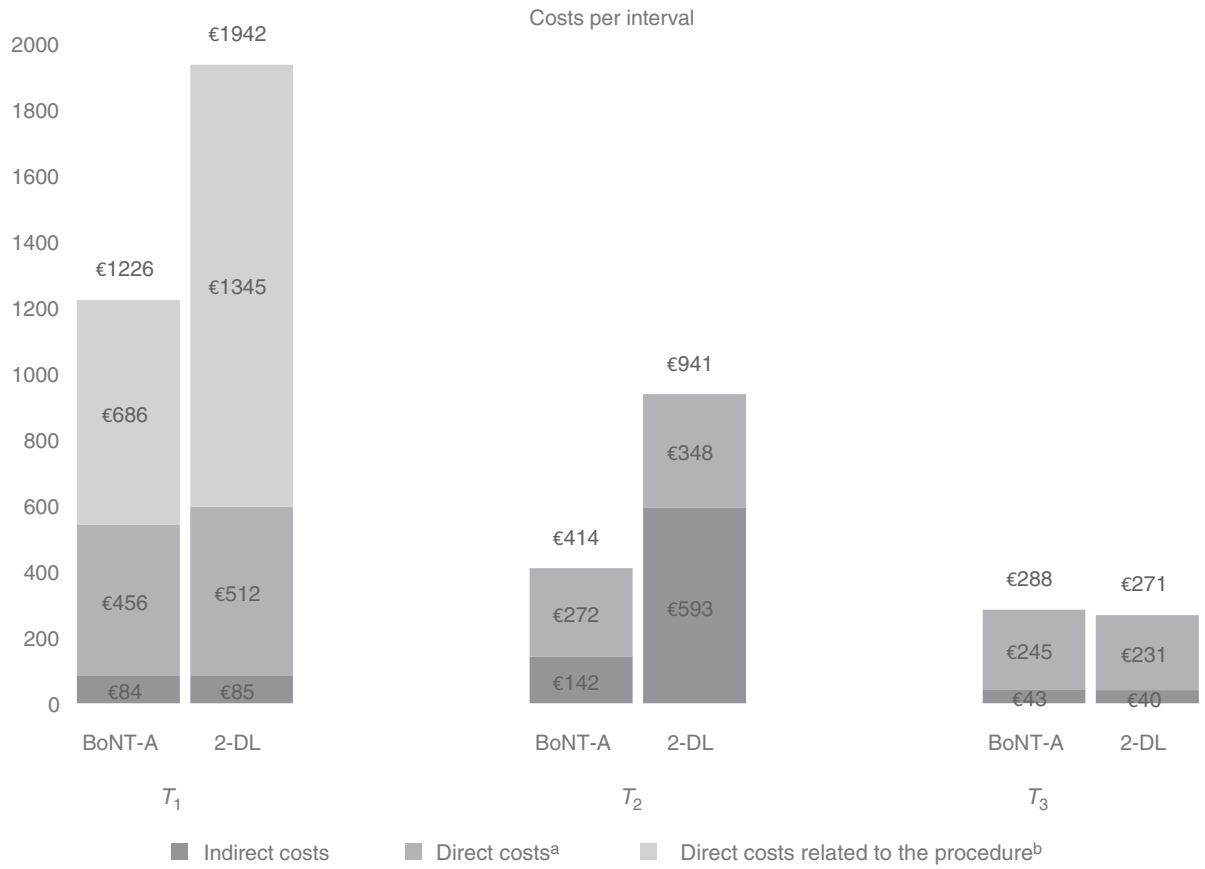

Figure 1: Overview of the direct and indirect costs made during the trial by time interval. [a]Direct costs include costs for the outpatient appointments, medication, and visits to the general practitioner or local hospitals. [b]Direct costs include costs for the surgical procedure, material, and visits to day clinics. Indirect costs include costs incurred by patients or caregivers for transportation, childcare, and sick leave. BoNT-A, botulinum neurotoxin A; 2-DL, two-duct ligation. [Colour figure can be viewed at wileyonlinelibrary.com]

duct ligation missed 23.5 hours (range 0–56, standard deviation 17.16).

In 92% of patients who received BoNT-A there was a desire for further treatment at 32 weeks, compared with 22% in the two-duct ligation group. Consequently, most of the patients treated with BoNT-A required a new preoperative assessment and thus increased average costs. These costs were, however, not included in the analysis.

DISCUSSION

This interventional, RCT-based analysis of cost-effectiveness for treating drooling demonstrates that two-duct ligation is more expensive than BoNT-A injections after one treatment cycle. This is (to some extent) offset by the fact that two-duct ligation is a more effective procedure: both treatment success and wish for subsequent treatment favoured two-duct ligation, which suggests that, despite its higher initial costs, it might be a more cost-effective treatment when considered over multiple treatment cycles.

The costs made during the follow-up visits were relatively similar, although this is also partly due to the trial protocol. Most children in the RCT visited an ear, nose, and throat consultant at the 8- and 32-week follow-up visits; however, in our routine clinical practice, patients who undergo BoNT-A injections will visit the rehabilitation physician preoperatively and follow-up is mainly coordinated by the speech and language therapists. This could have resulted in a slight overestimation of the costs after BoNT-A injection.

More caregivers in the two-duct ligation group reported having to take off work or hire child minders to care for their child in the first days after the intervention, which was a major driver of the difference in costs between the procedures. This difference is possibly linked to the larger invasiveness of the two-duct ligation procedure since the children in that group did experience more pain and discomfort than their peers in the BoNT-A group.[10] The duration of the procedure was the other major driver of the difference in costs between the procedures, which was reflected by the decrease in the ICER in the sensitivity analysis.

Wherever possible, general costs for health care resources were used. However, there were no general costs available for those associated with the interventions.

Therefore, a micro-costing approach was used to calculate the costs made in the operation room. Owing to micro-costing, we have presented a better outlook on the total costs per intervention which might make our results more applicable to other health care centres. However, it must be noted that normally in our centre the prices per operation room team are not activity-based and an average price for medication, materials, and disposables is included for all interventions.

The strength of this RCT is the prospective setup and the societal perspective approach, which includes the productivity loss of the caregivers. There are several limitations, however. The main one from the economic evaluation was that the questionnaire used was not validated for quality of life, so calculation of QALYs was not possible. This would be desirable in future research, as it would allow a comparison of the gain in quality-adjusted life-years with a willingness-to-pay threshold. Nor did we make use of a standardized ceiling ratio for the ICER. Therefore, we cannot determine whether two-duct ligation is more cost-effective than BoNT-A. However, the current data provide the first insight that lays the foundation for future analyses of cost-effectiveness.

Furthermore, there was no blinding to treatment allocation; however, the fact that blinded evaluation of a recorded drooling quotient was very closely matched to an unblinded drooling quotient suggests that this did not noticeably influence the outcome of the study.[10]

We performed a sensitivity analysis for the duration of surgery. It seems, however, that there are myriad other sources of potential variation in the cost structure which we did not assess.

A final limitation is the length of follow-up, especially because the wish for subsequent treatment was higher after BoNT-A injection.

The use of cost diaries gave some valuable insight into the indirect costs made in the first 2 weeks. Although we assume that the larger part of the productivity loss would occur during this period, we think that this study would have benefited from a longer registration of the cost diaries. However, one could speculate that compliance would reduce when extending the time horizon for a cost diary. For now, we can only partly assess the community costs directly related to the intervention. This might be an underestimation, as it is plausible that there would also have been loss of working hours during the baseline and follow-up visits during the whole treatment cycle.

Furthermore, one could speculate on the generalizability of our analysis of cost-effectiveness because this RCT was conducted in a single tertiary-care centre, in a single country. However, because of micro-costing, we present a better outlook on the total costs per intervention which might make our results more applicable to other health care centres. Moreover, ours is the only Dutch centre specializing in both treatments, so our analysis of cost-effectiveness is representative of the Dutch community.

In conclusion, this study presents the first insight into the costs included in the treatment of drooling. Drooling is a well-known problem with severe consequences. The use of BoNT-A injections is well established and although two-duct ligation has gained popularity, it is a relatively new, unknown treatment modality.[10,12,19] This article reveals that BoNT-A is slightly less expensive whereas there is a greater treatment response with a presumed longer-term effect after two-duct ligation, so its costs generally only have to be paid once for a 'lifetime solution'. The results in this study show that two-duct ligation is equal in costs after about 1.5 BoNT-A injections. We conclude that the additional cost of two-duct ligation is to some extent offset by a larger treatment success proportion than BoNT-A. Future research should, however, confirm this and focus both on the long-term costs and on the effect of both treatments over multiple cycles.[11,12]

ACKNOWLEDGEMENTS

We thank Peter Jongerius, who performed all the BoNT-A injections. We also thank Karen van Hulst, Marloes Lagarde, Sandra de Groot, Corrie Erasmus, Corinne Delsing, and Saskia Kok, who had a role in acquiring the data. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

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