PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	An open-label cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport®)
AUTHORS	Hefter, Harald; Benecke, Rainer; Erbguth, Frank; Jost, Wolfgang; Reichel, Gerhard; Wissel, Joerg

VERSION 1 - REVIEW

REVIEWER	Miguel Coelho, MD Department of Neurosciences Neurology Service Hospital de Santa Maria and Instituto de Medicina Molecular Lisbon, Portugal No competing interests
REVIEW RETURNED	29-Oct-2012

GENERAL COMMENTS	The paper by Hefter et al reports a secondary outcome from a prospective, open-label and multicenter study on the efficacy of a single cycle injection of Dysport 500 U for cervical dystonia. The secondary outcome is QoL and this is clearly stated in the manuscript. The data is very well reported and the results show that the treatment was efficacious in improving the QoL, using a well validated scale for cervical dystonia. Nevertheless, some points deserve a comment: 1) This is a non-controlled study and this must be mentioned in the methods section. 2) Assessment of primary outcome seems to have been done by the injector physician, and this should also be stated, as it may amplify treatment effect. 3) Baseline characteristics of study population should be reported in a table. 4) If this is a prospective study, why was Tsui not available for some patients at baseline? 5) The topic of psychoanaleptics drugs should be detailed: which drugs and how many patients were using them. 6) Safety data must be reported, even if in a briefer version than the original report of primary outcome. 7) It would be interesting to compare the improvement in CDQ-24 between patients with pain and no pain at baseline. 8) The correlation R between improvement in CDQ-24 and Tsui is weak. This should be discussed, and instead of being a limitation of the study, may suggest that QoL improves mainly due to other variables, and this is very interesting. 9) To better study the variables contributing to QoL, I suggest the authors do a logistic regression, using the CDQ-24 as the dependent

	variable. 10) The apparent discrepancy between total improvement of CDQ-24 at week 12 and the worsening of stigma at week 12 should be better discussed. 11) The report of the results correlating pain and Tsui scores improvement is not clear to read. Please re-write this. 12) The figures legend do not explain the meaning of the rectangle around some variables (day to day functions activity and stigma)

REVIEWER	Dr VIctoria Allgar Senior Lenturer Hull and York Medical School United Kingdom
REVIEW RETURNED	07-Jan-2013

THE STUDY	In the methodology there was no power cacluation presented. The patient group is one group of patients, with no control group. The main analysis is the change in scores from baseline to week 4, and baseline to week 12. It was not clear what statistical tests were undertaken. This type of data would lend itself to either ANCOVA to look at week 4 data adjusted for baseline, and week 12 data adjusted for baseline, or a repeated mesaures ANOVA to look at changes over time (baseline, week 4 and week 12), which would also allow comparison of groups e.g. torticollis and laterocollis. Simply using a change in score maybe misleading.
RESULTS & CONCLUSIONS	The data should be analysed using the methodology described above, which may or may not support the conclusions drawn.
REPORTING & ETHICS	A flow chart of the data would be useful.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
COMMENT: 1) This is a non-controlled study and this must be mentioned in the methods section.
RESPONSE: This has been added to the first line of Methods.
COMMENT: 2) Assessment of primary outcome seems to have been done by the injector physician, and this should also be stated, as it may amplify treatment effect.
RESPONSE: A statement to this effect has been added to the third paragraph of Methods. Additionally, this was addressed in the article already published from this study ([13] Hefter et al. BMJ Open 2011).
COMMENT: 3) Baseline characteristics of study population should be reported in a table.
RESPONSE: The baseline characteristics of the populations are included in the first three paragraphs of the Results section. Additionally, this data has been previously presented in Table 1 of reference 13. We have added a sentence stating this in the Results.
COMMENT: 4) If this is a prospective study, why was Tsui not available for some patients at baseline “and/or postbaseline assessments”?
RESPONSE: This sentence was reworded to avoid confusions: “Data of the Tsui rating scale at baseline (Visit 1) and at least one post-baseline visit (Visit 2 or 3) were available in 503 patients (ITT population)”, i.e. at least two assessments had to be available to include patients in the ITT population. Only one Tsui assessment was recorded for 12 patients and they were therefore excluded from the analyses.
COMMENT: 5) The topic of psychoanaleptics drugs should be detailed: which drugs and how many

patients were using them.
RESPONSE: The percentage of patients using psychoanaleptics is stated on page 9 (13.6%). All drugs were documented in the clinical database but a separate analysis was not planned. Since this is a small proportion of the patient population, we feel it is unlikely to have affected the outcome of the study.
COMMENT: 6) Safety data must be reported, even if in a briefer version than the original report of primary outcome.
RESPONSE: A brief summary of safety data has been included in the results. Readers will also be able to freely access the full safety data set in [13] as stated in the results.
COMMENT: 7) It would be interesting to compare the improvement in CDQ-24 between patients with pain and no pain at baseline.
RESPONSE: An improvement in pain is seen in all evaluated scores (Figures 1 and 2). As the CDQ-24 includes pain items, we would inevitably expect a change in the global score if we stratified to pain/no pain at baseline. For patients with no pain at baseline, the improvement in CDQ-24 would be less pronounced than for patients with pain at baseline.
COMMENT: 8) The correlation R between improvement in CDQ-24 and Tsui is weak. This should be discussed, and instead of being a limitation of the study, may suggest that QoL improves mainly due to other variables, and this is very interesting.
RESPONSE: This is discussed in the first paragraph of Discussion. We also included some additional text in this part of the Discussion to stress this interesting aspect.
COMMENT: 9) To better study the variables contributing to QoL, I suggest the authors do a logistic regression, using the CDQ-24 as the dependent variable.
RESPONSE: We have analysed the CDQ-24 in correlation with the Tsui score, different pain parameters (patient diary, global assessment) and the day-to day functions and activities. With the proposed analyses we would expect a ranking order of those factors influencing QoL mostly. The present data already show that all factors have an influence on CDQ-24 and it is difficult to say whether a logistic regression would add substantially to the available data. Beyond that, an analysis of this scale is not feasible in the time available for article revisions.
COMMENT: 10) The apparent discrepancy between total improvement of CDQ-24 at week 12 and the worsening of stigma at week 12 should be better discussed.
RESPONSE: There is an overall improvement in CDQ-24, but ‘stigma’ worsening correlates with Tsui score. This discrepancy is demonstrated in Fig. 1 with all subscores improving between weeks 4 and week 12, except Stigma. This discrepancy was also discussed in the Results and Discussion sections of the manuscript.
COMMENT: 11) The report of the results correlating pain and Tsui scores improvement is not clear to read. Please re-write this.
RESPONSE: The report of the results correlating pain and Tsui scores improvement was reworded to make it clearer.
COMMENT: 12) The figures legend do not explain the meaning of the rectangle around some variables (day to day functions activity and stigma)
RESPONSE: The rectangles were inserted in order to draw the reader’s attention to the fact that these data sets differed from the others. Scores worsened from Week 4 to Week 12 in the outlined category, but improved in all other categories. We have removed the rectangles and inserted an asterisk and footnote instead.

Reviewer 2:
COMMENT: In the methodology there was no power calculation presented.
RESPONSE: As mentioned by reviewer 1, this is a report on secondary outcomes. It is uncommon to perform power calculations for secondary study endpoints. As such, we have not presented it in this

article.
COMMENT: The patient group is one group of patients, with no control group.
RESPONSE: This is common for non-controlled studies. We have further highlighted this fact in the Methods section, as mentioned for point 1 of the first reviewer.
COMMENT: The main analysis is the change in scores from baseline to week 4, and baseline to week 12. It was not clear what statistical tests were undertaken. This type of data would lend itself to either ANCOVA to look at week 4 data adjusted for baseline, and week 12 data adjusted for baseline, or a repeated measures ANOVA to look at changes over time (baseline, week 4 and week 12), which would also allow comparison of groups e.g. torticollis and laterocollis. Simply using a change in score maybe misleading. The data should be analysed using the methodology described above, which may or may not support the conclusions drawn.
RESPONSE: The study previously published [13] includes a repeated-measures ANCOVA for the time course of Tsui total score improvement. For the analyses of the secondary outcomes presented in this manuscript, we had chosen a purely descriptive approach. The statistical methods are described in detail in the Methods part. Additionally, a subsequent publication is planned with further subgroup analyses on torticollis vs. laterocollis characteristics, which we do not want to speculate here.
COMMENT: A flow chart of the data would be useful.
RESPONSE: A flow chart of the study design or patient disposition was presented in Hefter et al 2011 [13], Figures 1 and 2. A table of baseline characteristics of the patient population is discussed in the first three paragraph\s of the results section. Alternatively, this was addressed in Table 1 of [13]