Inspiratory Muscle Training does not improve clinical outcomes in 3-week COPD rehabilitation: Results from a Randomised Controlled Trial

Online Supplement: Sample size, randomisation and missing values

Planned sample size

In a non-randomised pilot-study in the Clinic Bad Reichenhall, 49 patients received standard inpatient Pulmonary Rehabilitation (PR) in the control group (CG), and 70 patients received PR and an additional Inspiratory Muscle Training (IMT) in the intervention group (IG). We found a standardised mean difference of d=0.5 in change in PI_{max} in favour of the IG. Taking into account that this estimate may be biased in an unknown direction, we expected a conservative effect of d=0.3 between the IG and CG in change in PI_{max}. Setting Alpha=0.05 and Power=0.8, 176 patients per group (total n=352) are necessary to secure this effect (intention to-treat analysis). However, from previous studies and clinical experience we expected some patients to withdraw from the study before the end of inpatient rehabilitation, e.g. because of severe exacerbations. Furthermore, we used broader inclusion criteria than in most other IMT-studies (for example including patients with exacerbations immediately before the start of the inpatient rehabilitation) which might increase the number of withdrawals. Therefore, we expected that up to 20% of the included rehabilitation patients might withdraw from the study. Therefore, to complement the intention-to-treat analysis with an as-treated analysis, we planned to include a total of 420 patients in the study.

Total sample size after completed recruitment

More eligible patients could be recruited faster than we had assumed at the start of the study. The high heterogeneity of the sample in comparison with samples in other studies on IMT (for example by including patients with exacerbation immediately prior to PR), may lower statistical efficacy. After we had recruited 420 patients (in 04/2014), we decided to continue with the study as planned to enhance power for the planned secondary analyses (for example, moderator analyses). In the end, a total of 611 patients could be recruited.

Randomisation

The randomisation list was created in SPSS at the University of Wuerzburg. In a first step, block-randomisation with one block was used to allocate 420 patients (planned sample size) to the IG and CG.

After the decision to increase sample size, an additional block of 300 (possible) patients was randomized to IG and CG. The randomisation list was sent to the Clinic Bad Reichenhall. There, it was transformed into an excel table. A macro was programmed that ensured that the treating physicians saw the ID of the patient to be included (after the patient's informed consent and inclusion in the study). This macro was programmed in such a way (accurate to the second) that for the including physician, only the ID of the patient to be randomised was visible. This ensured that no double assignment to an ID was possible. Only when the patient was included and an ID was given, the programme showed the assignment (IG / CG). This operation could not be undone. Therefore, the group allocation could not be manipulated by the physicians.

Missing values

Missing data emerged for two reasons: (1) discontinuation of PR (i.e. no data available at T1) and (2) missing data in some variables (0-3% per variable). We assumed that the missing data were missing completely at random or missing at random. All missing data were imputed on the item level with the multiple imputation procedure implemented in SPSS V23 (Markov Chain Monte Carlo procedure). All variables were used as both dependent and predictor variables. For categorical variables, a (multinomial) logistic model was used and for continuous variables, a linear regression model was used. Ordered categorical (ordinal) variables were treated as continuous variables. We created 10 imputed data sets. We used this strategy two times: (1) for the ITT-Analyses, including N=602 patients and (2) for the PP-analyses, including N=561 patients. Therefore, we created 10 imputed data sets for the ITT-analyses and 10 imputed data sets for the PP-analyses.

Statistical analyses were done using statistic software R. Pooled results of descriptive parameters (for example means) were computed via the R-package "mice" (van Buuren, 2011). Pooled results of the ANCOVA analyses were computed with the Zelig-package (Choirat et al, 2015). The TDI could not be imputed due to the scaling of the items, thus listwise deletion was applied.

References

Choirat C, Honaker J, Imai K, King G and Lau O (2015). *Zelig: Everyone's Statistical Software*. Version 4.2-1, http://zeligproject.org/.

van Buuren, S. & Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software, 45(3), 1-67. URL http://www.jstatsoft.org/v45/i03/.