Clin Oral Invest (2007) 11:307–310
DOI 10.1007/s00784-007-0099-y

SHORT COMMUNICATION

A bivariate multi-level model, which avoids mathematical coupling in the study of change and initial periodontal attachment level after therapy

Hans-Peter Müller

Received: 15 October 2006 / Accepted: 10 January 2007 / Published online: 31 January 2007
© Springer-Verlag 2007

Abstract When relating the change of periodontal attachment level to its baseline value, mathematical coupling has to be taken into account. Oldham's strategy of testing the differences in variances of two repeated measurements was recently advocated as a possible solution. Here, a simple bivariate three-level (site and subject with a lowest level specifying the multivariate structure) model is introduced where gingival units (sites) were nested in subjects. It allows the easy interpretation of the variance–covariance structure and fixed model estimates, and provides an unbiased estimate of the correlation between the mean and change of periodontal measurements. The properties of this model are exemplified using data of a study on the clinical effects of non-surgical periodontal therapy in adults. Based on the covariance terms, correlation between the change in clinical attachment after therapy and the mean of the pre-operative and post-operative attachment level was very low (about −0.11, $p<0.001$) at the site level, and not significant at the subject level. Regarding the attachment level, differential treatment effects may be neglected. With regard to periodontal probing depth, however, patients with larger extent and severity would benefit more from treatment. The present communication provides an easy strategy for the avoidance of mathematical coupling in the study between change and initial value by employing a bivariate multi-level model.

Keywords Mathematical coupling · Oldham's strategy · Phase I periodontal therapy · Periodontal probing · Multivariate multi-level modelling

H.-P. Müller (✉)
Faculty of Dentistry, Kuwait University,
P.O. Box 24923, Safat 13110, Kuwait
e-mail: hp.muller@hsc.edu.kw

Introduction

When relating the change of a measurement after therapy to its baseline value, for example, pre-operative and post-operative periodontal probing measurements, mathematical coupling has to be taken into account. Several strategies for avoiding mathematical coupling were recently reviewed [10]. A univariate multi-level solution had been suggested [1]. When applying this approach to periodontal data, the difference between pre-operative and post-operative measurements and their respective mean (a strategy similar to that proposed by Bland and Altman [2] when assessing the agreement between two methods) may be specified as repeated measures at level 1 nested in higher levels (sites, subjects). To accomplish this, a centred covariate indicating examination occasion has to be introduced. An advantage to simple correlation analysis between mean values and change is that additional covariates may simultaneously be considered [1]. As long as the response variable cannot be derived from covariates, mathematical coupling is no longer an issue. However, apart from an unbiased correlation estimate between change and mean value, interpretation of model estimates seems to be overly complicated. In this study, as suggested by Rasbash and Goldstein [9], a simple bivariate three-level model is introduced where sites are nested in subjects. It allows the easy interpretation of the variance–covariance structure and fixed model estimates, and provides an unbiased estimate of the correlation between the mean and change of periodontal measurements.

The bivariate multi-level model

The bivariate response data, i.e. change in periodontal measurement after therapy, and mean of pre-operative and post-operative measurement, are incorporated in a multilevel model by creating an extra level below the original level 1 units (sites) to define the multivariate structure [4, 7]. The three-level model can then be written as:

$$y_{ijk} \sim N(XB, \Omega),$$

$$y_{ijk} = \beta_0 z_{1ijk} + \beta_1 z_{2ijk} + \sum_{n=2}^{m} \beta_n z_{1ijk} x_{n,ijk} + \sum_{n=2}^{m} \beta_n z_{2ijk} x_{n,ijk} + v_{1k} z_{1ijk} + v_{2k} z_{2ijk} + u_{1jk} z_{1ijk} + u_{2jk} z_{2ijk}$$

$$z_{1ijk} = \left\{ \begin{array}{c} 1 \text{ if change} \\ 0 \text{ if mean} \end{array} \right\}, z_{2ijk} = 1 - z_{1ijk}$$

$$\begin{bmatrix} v_{0k} \\ v_{1k} \end{bmatrix} \sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix} \sigma^2_{v0} & \\ \sigma_{v01} & \sigma^2_{v1} \end{bmatrix}$$

$$\begin{bmatrix} u_{0jk} \\ u_{1jk} \end{bmatrix} \sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix} \sigma^2_{u0} & \\ \sigma_{u01} & \sigma^2_{u1} \end{bmatrix}$$

Estimates for the change and mean are given by the β_0 and β_1 coefficients, respectively. There is no level 1 variation specified because it solely exists to define the multivariate structure. The level 2 variances $\left(\sigma^2_{u0}, \sigma^2_{u1}\right)$ are the between-sites variances with covariance σ_{u01}. This will give an unbiased estimate of the correlation between change and mean probing parameter, calculated as $r_{u01} = \sigma_{u01} \Big/ \sqrt{\sigma^2_{u0} \times \sigma^2_{u1}}$. The level 3 variances $\left(\sigma^2_{v0}, \sigma^2_{v1}\right)$ are between-subject variances with covariance σ_{v01}. The model contains covariates x_m, which might influence either response in the bivariate model. This multivariate response model can easily be set up, for example, in *MLwiN* 2.0 (Center of Multilevel Modelling, Bristol, UK).

Example

To illustrate the properties of this model, data of a previously published study [6] on the clinical effects of non-surgical periodontal therapy in adults was used. In brief, ten systemically healthy adults with chronic periodontitis were enrolled in the initial (hygienic) phase of periodontal therapy. Four weekly sessions consisted of oral hygiene instruction, and supra-gingival and sub-gingival scaling and root planing, which was done in 2–4 sessions of 30 min each under local anaesthesia. Patients rinsed thereafter twice daily for 2 weeks with a 0.1% solution of chlorhexidine digluconate. Before and 6 weeks after the completion of initial therapy, clinical examinations at 6 sites of each tooth present were carried out including

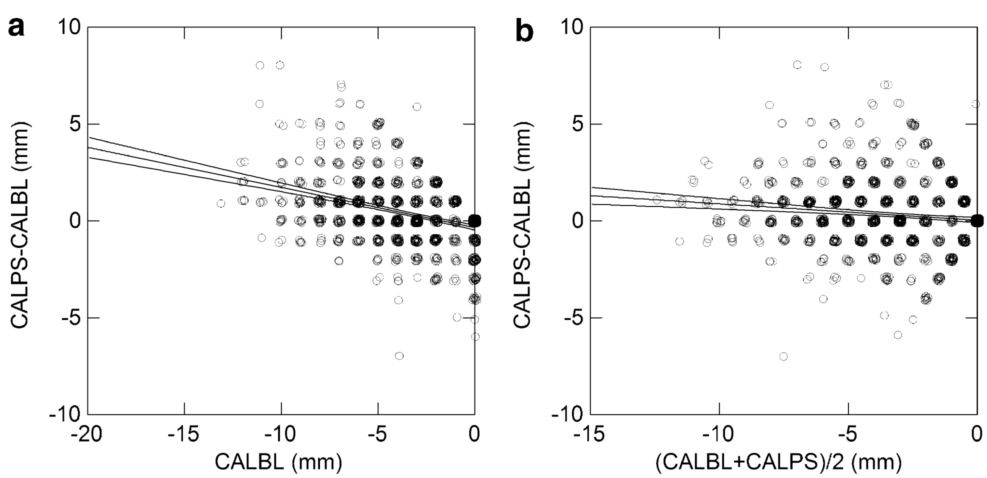

Fig. 1 **a** Scatter plot of the change in clinical attachment loss, CALPS−CALBL, on the baseline clinical attachment loss, CALBL. Regression line and 95% confidence band. 1,505 observations were made in 10 patients. **b** Scatter plot of the change in clinical attachment loss, CALPS−CALBL on the mean of the pre-operative and post-operative clinical attachment loss, (CALBL+CALPS)/2. The near-zero correlation between change and average points to only slightly better results in more severely affected sites (in terms of attachment loss) after treatment

Table 1 Bivariate three-level variance components model for the response change, and mean of the clinical attachment level and periodontal probing depth

Note that the lowest level defines the multivariate structure. The parameter estimates with standard error are in the *first parentheses*. The correlations are in the *second parenthesis*.

	Parameter	Clinical attachment level	Periodontal probing depth
Fixed part	β_0	0.269 (0.117)	−0.599 (0.162)
	β_1	−3.019 (0.467)	2.921 (0.155)
Random part			
Subject level	σ^2_{v0}	0.120 (0.061)	0.251 (0.118)
	σ_{v01}	−0.235 (0.188) (−0.464)	−0.185 (0.099) (−0.784)
	σ^2_{v1}	2.136 (0.973)	0.222 (0.107)
Site level	σ^2_{u0}	2.218 (0.081)	1.586 (0.058)
	σ_{u01}	−0.362 (0.089) (−0.106)	−0.675 (0.053) (−0.349)
	σ^2_{u1}	5.282 (0.193)	2.364 (0.086)

gingival and plaque indices, probing depth, clinical attachment level, and bleeding on probing. In the previous article, logistic regression analyses using generalised estimating equations [3] revealed that clinically relevant gain or loss of attachment, i.e. 2 mm or more, mainly depended on the clinical conditions at the outset and after scaling.

If the hierarchical structure of the data was disregarded, change in clinical attachment was moderately correlated with the initial attachment level, $r=-0.403$, $p<0.001$. Figure 1a apparently indicates that the more severe periodontitis at baseline, the better the treatment response, i.e. gain of attachment. However, because one variable (baseline attachment level) consists of a part of the other variable (change in attachment level), this correlation is mainly due to mathematical coupling. When change is regressed on average between pre-operative and post-operative measurements (Fig. 1b), correlation is reduced to −0.157. As shown in the left part of Table 1, a variance components, bivariate (mean of baseline and post-operative level of attachment; change of measurement), three-level model (with site and subject as higher levels) without any further covariates revealed an estimate of change of 0.269 (standard error 0.117) mm while the estimate of the mean of pre-operative and post-operative attachment loss was −3.019 (0.467) mm. The variance/covariance matrix indicated, at the site level, a low, albeit still highly significant ($p<0.001$) covariance of −0.362 (0.089), which corresponds to a correlation coefficient (between change and mean of pre-operative and post-operative measurement) of $r=-0.106$. At the subject level, the correlation between change in clinical attachment and mean of measurement before and after therapy was considerably higher, $r=-0.464$, but not significant. Observations for periodontal probing depth were somewhat different (Fig. 2). The right part of Table 1 indicates that at the site level, the correlation between change and mean value of pre-operative and post-operative measurement was substantial, $r=-0.349$ ($p<0.001$). At the subject level, it was as high as −0.784 ($p<0.07$).

Discussion

In everyday periodontal practice, it is a most trivial fact that the deeper a periodontal pocket, the better the expected therapeutic result in terms of pocket depth reduction and gain of clinical attachment. Suppose, for example, that normal periodontal probing depths after treatment of periodontitis are within 3 or 4 mm. If that endpoint is to be achieved, deeper sites will benefit more from therapy, in

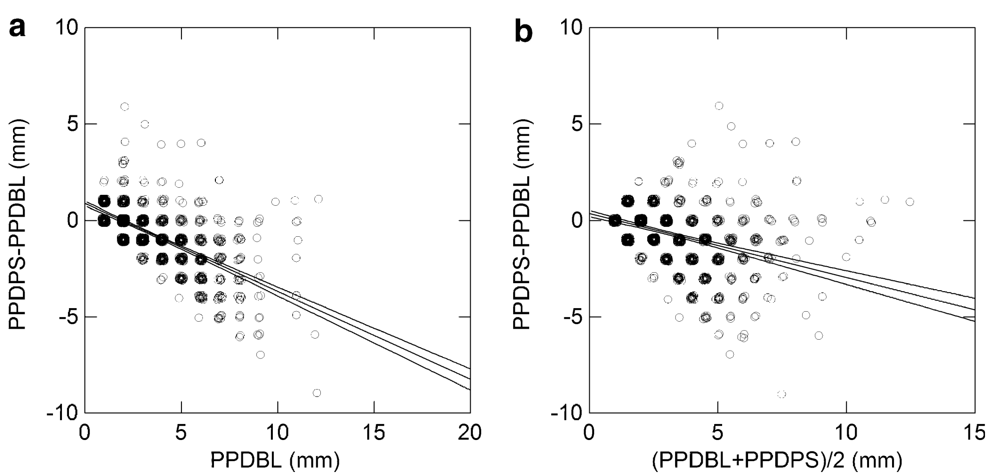

Fig. 2 a Scatter plot of the change in periodontal probing depth, PPDPS−PPDBL, on the baseline periodontal probing depth, PPDBL. **b** Change in the periodontal probing depth, PPDPS−PPDBL on the mean of the pre-operative and post-operative periodontal probing depth, (PPDBL+PPDPS)/2. The clear correlation between change and average points to better results in more severely affected (deeper) sites after treatment terms of change in pocket depth, than shallow sites. Moreover, because attachment gain can only occur at sites where it was lost due to disease, it won't be possible to detect gain after therapy in either shallow sites or sites with gingival enlargement [6]. The consistent observation of severity of periodontal disease mainly predicting improvement after therapy is an important issue in decision making for different treatment modalities. For example, periodontal flap surgery leads usually to loss of clinical attachment if conducted at sites with a periodontal probing depth of, say, less than 5 mm, while attachment gain can be expected if it is performed in deeper sites. In contrast, less invasive therapies such as scaling and root planing can be done at sites of, say, 3 mm without increasing the risk of loss of attachment [5]. Finally, if factors were to be identified in multiple regression analysis, which might influence the post-operative periodontal outcome, the model may be 'adjusted' for initial or baseline data. That the initial value then most probably turns out to be of major impact should not be a surprise after all. There is, however, another phenomenon, which has to be taken into account when interpreting such a result. For the special case that pre-operative and post-operative measurements have equal variances and measurement errors, it can be shown that due to mathematical coupling, a spurious negative association with a correlation coefficient of $-1/\sqrt{2} \approx -0.7$ will be observed even if the initial periodontal attachment level and change are not correlated at all [1, 10]. Heterogeneity in treatment response and/or measurement error may further exacerbate the effect of mathematical coupling. A practical solution for the problem is to relate change not to the initial value but rather to the average of pre-operative and post-operative measurements (Figs. 1b and 2b). Provided equal variances and measurement errors, differences and sums of measurements are unrelated and mathematical coupling does not occur; a concept, which had been proposed by Oldham [8]. The correlation between change and average of repeated measurements may indeed be used for testing differences in the variances of the repeated measurements themselves [10]. If, for example, treatment leads to better results in more severely affected sites, this would manifest itself in a lower variance of post-operative measurements, which in turn will lead to non-zero correlation between change and average. An elegant geometrical representation of Oldham's strategy was recently published by Tu and Gilthorpe [10].

It has to be stressed that to obtain the correct fixed and random estimates, the hierarchical data here requires at least another level to be considered, which is the subject. At the site level, the correlation between change and average clinical attachment level was very low, about 0.1, and not significant at the subject level. Thus, the differential treatment effect may indeed be neglected. A somewhat different picture emerged when periodontal probing depth was considered. Here, at the site level more severe disease clearly led to better outcome. In addition, subjects with greater extent and severity of periodontitis may also benefit more from treatment.

Covariates as, for example, gender, treatment arms, or site-specific and average plaque index, may be introduced into the model. However, indirect mathematical coupling may prevent entertaining covariates, which contain parts of the response variables.

Acknowledgement Supported by the Kuwait University Research Administration, Grant #DS04/02.

References

1. Blance AJ, Tu YK, Gilthorpe MS (2005) A multilevel modeling solution to mathematic coupling. Stat Methods Med Res 14:553–565
2. Bland JM, Altman DG (1986) Statistical methods assessing agreement between two methods of clinical measurement. Lancet i (8476):307–310
3. Diggle PJ, Heagerty P, Liang KY, Zeger SL (2002) The analysis of longitudinal data, 2nd edn. Oxford University Press, Oxford
4. Goldstein H, Browne WJ, Rasbash J (2002) Multilevel modelling of medical data. Stat Med 21:3291–3315
5. Heitz-Mayfield LJA, Trombelli L, Heitz F, Needleman I, Moles D (2002) A systematic review of the effect of surgical debridement vs. non-surgical debridement for the treatment of chronic periodontitis. J Clin Periodontol 29(Suppl 3):92–102
6. Müller HP, Heinecke A (2004) Clinical effects of scaling and root planing in adults infected with *Actinobacillus actinomycetemcomitans*. Clin Oral Investig 8:63–69
7. Müller HP, Stadermann S (2006) Multivariate multilevel models for repeated measures in the study of smoking effects on the association between plaque and gingival bleeding. Clin Oral Investig 10:311–316
8. Oldham PD (1962) A note on the analysis or repeated measurements of the same subjects. J Chronic Dis 15:969–977
9. Rasbash J, Goldstein H (2004) Mathematical coupling: a simpler approach. Int J Epidemiol 33:1401–1402
10. Tu YK, Gilthorpe MS (2007) Revisiting the relation between change and initial value: a review and evaluation. Stat Med 26:443–457

Copyright of Clinical Oral Investigations is the property of Springer Science & Business Media B.V. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.