

Application of multilevel growth-curve analysis in cancer treatment toxicities: the exemplar of oral mucositis and pain

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Abstract:

Purpose/Objectives: To introduce the use of a statistical technique known as multilevel growth-curve analysis and illustrate how the method can be advantageous in comparison with traditional repeated measures for the study of trajectories of signs and symptoms in individual patients over time.

Data Sources: Data were derived from use of the technique in a randomized clinical trial of a psychoeducational intervention to reduce severity of oral mucositis and oral pain.

Data Synthesis: The development of new biologic models that seek to explain clustering of signs and symptoms or the appearance and resolution of signs and symptoms motivates the need to use more sophisticated statistical techniques to test such models.

Conclusions: The application of multilevel growth model to an existing data set demonstrates that the model can be effective in the study of individual differences in trajectories of change in signs and symptoms.

Implications for Nursing: This method for the study of changes in patients' signs and symptoms over time can be of particular interest to nursing, both from a clinical point of view and as a way to test theoretical models that have been proposed to capture patient experiences with signs and symptoms.

Article:

The study of symptom clusters has become an important focus of oncology nursing research (Barsevick, 2007). Concurrently, longitudinal studies of clinical phenomena in which individuals are measured across time have become common. As the study of symptom clusters has matured, research has evolved beyond describing symptom clusters to questioning the underlying processes that lead to symptom clusters. These changes in research foci have led to biologic models of symptom clustering (Lee et al., 2004; Sonis, 2004a, 2004b) and a need for sophisticated statistical methods to test such models.

Lee et al. (2004) proposed a general inflammatory model in which cancer therapies (chemotherapy or radiotherapy) lead to the release of cytokines that, in turn, generate specific clusters of symptoms in patients receiving treatment. In a model specific to oral mucositis (OM), Sonis (2004b) proposed a pathobiologic model of OM that models the development and resolution of that serious side effect of cancer therapy. Linkage of these models and related models represents an important development in symptom cluster research. Both of the biologic models propose a longitudinal chain of processes that underlie the clinical phenomena under study. For the science to progress, researchers must use statistical methods that can appropriately model individual trajectories of change, capture interindividual variability in change over time inherent in the models, and model factors that explain that variation.

The traditional repeated-measures analysis of variance (ANOVA), which uses ordinary least-squares estimation, has long been the mainstay for statistical analyses of longitudinal clinical trials with continuous outcomes (Maxwell & Delaney, 2004). Repeated-measures ANOVA is highly effective in studying mean change and

treatment group differences in mean change over a limited number of occasions with balanced data. However, it is less useful for the study of interindividual variability in trajectories of change that practitioners commonly see in clinical settings, specifically in the context of signs and symptoms related to cancer treatment. An alternative to traditional repeated-measures ANOVA is one of several growth-curve modeling approaches to examine interindividual variability in trajectories of change. One commonly used method is the multilevel growth model in which observations (sign or symptom severity) over time are "nested" within a patient. The patient's trajectories of change then are linked to patient-related characteristics (e.g., age, gender) or treatment-related characteristics (e.g., radiation dose) that can be thought of as correlates of change.

The purpose of this article is to introduce growth-curve modeling of longitudinal data via the use of multilevel modeling and to illustrate the advantages of multilevel modeling with longitudinal clinical data over the traditional repeated-measures ANOVA model. It focuses on inter individual differences in trajectories of OM, a significant side effect of cancer therapy (Peterson, Keefe, Hutchins, & Schubert, 2006; Sonis et al., 2004).

Oral Mucositis

The current pathobiologic model of OM supports variations in clinical expression and is supported by substantial basic and clinical research (Sonis, 2002). Multilevel growth-curve models have the potential to integrate patient-based variations in clinical expression of OM within the pathobiologic model. Selected patient cohorts, including those receiving head and neck radiation (Elting, Cooksley, Chambers, & Garden, 2007) or hematopoietic stem cell transplantation (HSCT) (Sonis et al., 2004), typically demonstrate predictable peaks and troughs in severity of OM. However, distinct differences in the expression of signs and symptoms often occur across patients, even among those receiving similar treatment regimens, such as high-dose chemotherapy in preparation for stem cell transplantation. The variation may be seen in different trajectories of oral mucosal injury over time (the peaks and troughs noted previously) across individual patients. Such variation can include incidence and duration of clinically significant oral mucosal injury and can affect dose delivery of multi-cycle chemotherapy (Peterson, Jones, & Petit, 2007). In addition, the number of patients with solid tumors who experience OM is substantially higher than the number of patients undergoing head and neck radiation and HSCT combined (Avritscher, Cooksley, & Elting, 2004; Elting et al., 2003). In this model, clinical changes in oral tissue occur because of an underlying biologic process; also, individual trajectories of change are quite variable, and the variability may be the result of a host of patient-related (e.g., age, oral health) and treatment-related (e.g., type of treatment regimen) factors. To test model-related hypotheses, a statistical model must quantify individual trajectories of change and correlate the trajectories to patient-related and treatment-related variables. It also must have the potential to relate changes in one sign or symptom to patterns of change in other signs or symptoms (as a researcher might do in a study of symptom clustering over time). The multilevel growth model discussed in this article is one statistical model that is consistent with those requirements.

Multilevel Growth Models

Multilevel Growth Models in the Study of Oral Mucositis

A need exists for novel analytic approaches designed to integrate the modeling of OM among individual patients, vis-a-vis the collective patient experience, by quantifying individual trajectories of oral mucosal injury over time. As more and more researchers employ repeated-measure, longitudinal designs to study cancer signs and symptoms, the authors anticipate that the availability of longitudinal data will create a shift toward the use of new models for the study of change. The technique described in this article, multilevel growth-curve modeling, is one commonly used approach to the study of change over time.

Multilevel growth-curve modeling also can contribute to an enhanced understanding of the OM experience within a constellation of signs and symptoms in patients undergoing high-dose cancer therapies. The concept of symptom clusters has emerged as an important paradigm in oncology (Barsevick, 2007; Dodd, Miaskowski, & Paul, 2001; Kim, McGuire, Tulman, & Barsevick, 2005; Lee et al., 2004; Miaskowski & Aouizerat, 2007). In

that context, OM pathogenesis and clinical outcomes could be contributory to, or an outcome of, molecular-based toxicities such as fatigue associated with tumor necrosis factor-[alpha], interleukin (IL)-6, IL-8, and epidermal growth factor (Lee et al.). The symptom clusters can exhibit considerable variation across patients with cancer, even among those receiving comparable treatment regimens. Multilevel growth-curve modeling may help to elucidate and integrate data on OM with data related to the collective symptom experience across patients.

Statistical Basis

The methods presented herein are based on the seminal work by Bryk and Raudenbush (1992) and subsequent work of numerous methodologists (Curran, 2000; Singer & Willett, 2003; Verbeke & Molenberghs, 2000). A number of approaches to growth-curve modeling exist. Multilevel growth-curve modeling is used commonly because it is generalizable to other approaches, such as individual growth-curve modeling or latent curve growth-curve modeling. The approaches share a common statistical model discussed in detail later.

As the name suggests, a multilevel model consists of a number of hierarchically nested regression models in which model parameters (i.e., regression coefficients, standard errors, variance components, and covariance components) are computed simultaneously. Typical longitudinal multilevel modeling involves two different levels of equations: level 1 and level 2. The level 1 equations capture within-subject variability, in this case individual change over time, whereas level 2 equations capture between-subject variability. The authors describe both levels of equations in the following sections. After the authors present the statistical model, they discuss how the statistical model relates to the symptom experience over time in a sample of patients.

Level 1 equations: In the level 1 equation, each individual subject's change over time is a separate regression equation. In other words, each subject's outcome on the dependent variable(s) (erythema and pain in this example) is regressed onto the variable of time of measurement (e.g., day 1, day 2, day 3). The result is a regression equation (which may be linear or nonlinear) that represents each individual subject's growth curve. The coefficients that make up the regression equation are the individual subject's growth-curve parameters. With standard Cartesian coordinates, the Y intercept is the value in the outcome variable where the growth curve (either individual or group mean) intersects the abscissa axis (typically at a baseline day = 0). The linear rate of growth is termed slope, which is the amount of change in the dependent variable per unit of time. A quadratic term describes the amount of acceleration or deceleration (nonlinear increase or decrease) of the same dependent variable per unit of time squared.

Equation 1 is the general level 1 regression equation that captures individual change over time in some outcome (in this case, the authors used erythema to illustrate the process). Unlike repeated-measures ANOVA, which aggregates information and loses individual differences, multilevel models retain individual information and develop separate regression equations for each subject. The subscript "i" indicates an individual. The subscript "t" indicates time, which could be actual days from a baseline zero or, as more commonly encountered in clinical research, an ordinal series of time (e.g., first treatment, second treatment).

Equation 1: $[Y_{.sub.ti}] = [[\pi]_{.sub.0i}] + [[\pi]_{.sub.1i}] [[\alpha]_{.sub.ti}] + [[\pi]_{.sub.2i}] [[\alpha]_{.sub.ti}^{sup.2}] + [[\epsilon]_{.sub.ti}]$

From equation 1, $[Y_{.sub.ti}]$ is subject i's erythema score at measurement t; $[a_{.sub.ti}]$ is the day of measurement postchemotherapy (e.g., 0, 1, 2, 3) for the erythema score and represents linear change. The $[[\alpha]_{.sub.ti}^{sup.2}]$ term is the time of measurement squared and represents curvilinear change over time. $[[\epsilon]_{.sub.ti}]$ is the difference between the observed erythema score at time t for subject i ($[Y_{.sub.ti}]$) and the predicted erythema score. $[[\epsilon]_{.sub.ti}]$ is a residual value that indicates an individual subject's variability. Because the authors must estimate a separate level 1 equation for each subject, the timing of measurement occasions and the number of measurement occasions may vary over subjects. Thus, multilevel models can handle unbalanced designs as opposed to traditional repeated-measures ANOVA. Unbalanced

designs refer to data collection processes in which the number of measurement occasions differs from one patient to another. The discrepancy may be a result of missing data or duration of treatment regimen conditions that often are encountered in longitudinal clinical studies. The ability to handle varying times of measurement and number of measurement occasions is critical in the longitudinal study of clinical phenomena.

Each subject's level 1 equation, called a growth curve, consists of a function of growth parameters: a Y intercept, $[\pi]_{.0i}$; a slope, $[\pi]_{.1i}$; a quadratic term, $[\pi]_{.2i}$; and an error term, $[\epsilon]_{.ti}$. The Y intercept, $[\pi]_{.0i}$, is an individual subject i 's predicted erythema score where time is zero (i.e., $[a]_{.ti} = 0$). Y intercepts are estimated and interpreted where the other variables in the equation are set to zero (Biesanz, Deeb-Sossa, Papadakis, Bollen, & Curran, 2004; Cohen, Cohen, West, & Aiken, 2003; Wainer, 2000). The linear change rate, or slope of the growth curve for individual subject i , is $[\pi]_{.1i}$. The slope is the predicted linear rate of change in erythema scores per unit of time, t . In the quadratic model, the slope has a special meaning. It is the rate of change at the intercept. That is, it is the slope of the line passing through the intercept and tangent to the curve represented by the quadratic term (Singer & Willett, 2003). The quadratic growth parameter for subject i is $[\pi]_{.2i}$, and it is the rate of acceleration (or deceleration if negative) in erythema scores per unit of time squared, $[t]_{.sup.2}$.

To illustrate the Y intercept and slope concepts, Figure 1 shows a linear growth curve fitted to a hypothetical subject's erythema scores for the first four time points (day 0, day 1, day 2, and day 3) using the equation described earlier. For simplification purposes, the figure does not show the quadratic term. The circles represent the measured erythema score at days $t = 0, 1, 2,$ and 3 , and the dotted line is the subject's growth curve. The Y intercept, $[\pi]_{.0i}$; slope, $[\pi]_{.1i}$; and residuals, $[\epsilon]_{.ti}$, for the subject's growth curve are labeled.

Level 2 equations: Estimation of the growth parameters (i.e., intercept, slope, and quadratic term) in level 1 equations involves a different set of regression equations. Each growth parameter is modeled by a regression equation that captures the population main effect plus the variability resulting from each individual. The level 2 equations for the current example consist of three regression equations. As shown here, equation 2 examines subjects' intercept values, equation 3 estimates subjects' linear slope parameter values, and equation 4 estimates subjects' quadratic parameter values.

$$\text{Equation 2: } [\pi]_{.0i} = [\beta]_{.sub.00} + [\mu]_{.sub.0i}$$

$$\text{Equation 3: } [\pi]_{.1i} = [\beta]_{.sub.10} + [\mu]_{.sub.1i}$$

$$\text{Equation 4: } [\pi]_{.2i} = [\beta]_{.sub.20} + [\mu]_{.sub.2i}$$

Recalling equation 1,

$$[Y]_{.sub.ti} = [\pi]_{.sub.0i} + [\pi]_{.sub.1i} [\alpha]_{.sub.ti} + [\pi]_{.sub.0i} [\alpha]_{.sub.ti}^{sup.2} + [\epsilon]_{.sub.ti}$$

the authors substitute the $[\beta]$ s and $[\mu]$'s for the growth parameters to yield equation 5.

$$[Y]_{.sub.ti} = ([\beta]_{.sub.00} + [\mu]_{.sub.0i}) + ([\beta]_{.sub.10} + [\mu]_{.sub.1i})[\alpha]_{.sub.ti} + ([\beta]_{.sub.20} + [\mu]_{.sub.2i}) + [\epsilon]_{.sub.ti}$$

Figure 2 shows a hypothetical grand mean linear growth curve shown as a solid line with the individual subject's growth curve shown as a dashed line. The coefficients of the level 2 equations are labeled.

Figure 2 illustrates the relationship between the individual's trajectory of erythema and the mean (across all individuals) trajectory of erythema. In the figure, the dashed line is identical to the line portrayed in Figure 1. The solid line in Figure 2 portrays the mean trajectory, and the parameters of interest include the parameters for the mean trajectory (the $[\beta]$ terms) as well as the parameters for the deviation of the individual from the mean (the $[\mu]$ terms). The parameters are described in the following sections.

$[\beta]$ -terms fixed effects: Three $[\beta]$ terms exist: $[[\beta].sub.00]$, $[[\beta].sub.10]$, and $[[\beta].sub.20]$. In repeated-measures ANOVA terminology, the terms represent population main effects. In growth-modeling terminology, $[[\beta].sub.00]$ is the grand mean intercept. The interpretation of this mean intercept for growth modeling is different from repeated-measures ANOVA, which interprets the intercept as the value aggregated across all subjects and all time points. Therefore, it is the average value of erythema regardless of time. For growth modeling, the intercept typically is set to represent the initial or beginning value of the dependent variable at time 0 ($[[\alpha].sub.ti] = 0$). The statistical testing of $[[\beta].sub.00]$ determines whether the intercept value differs from zero. Other interpretations of the intercept can be accomplished by centering the data on a time point that is not zero. For example, if the time variable was centered on the mean time value, in the current example 1.5 days ($[[\alpha].sub.ti] = 1.5$), then the intercept would be consistent with the repeated-measures ANOVA results, because the mean intercept value would be calculated at the mean time value. $[[\beta].sub.10]$ is the grand mean slope, or average linear rate of change per unit of time for the population growth curve. Testing $[[\beta].sub.10]$ against zero is similar to orthogonal linear contrasts in repeated-measures ANOVA terminology (Biesanz et al., 2004). $[[\beta].sub.20]$ is the grand mean quadratic term, or average change in slope value per squared unit of time.

$[\mu]$ -terms random effects: Figure 2 illustrates two random coefficients: $[[\mu].sub.0i]$ is the random coefficient for the intercept, whereas $[[\mu].sub.1i]$ is the random coefficient for slope. The term $[[\mu].sub.0i]$ is the difference between the individual's Y intercept ($[[\pi].sub.0i]$) and the overall grand mean intercept ($[[\beta].sub.10]$), whereas the term $[[\mu].sub.1i]$ is the deviation between the individual's slope and the overall grand mean slope ($[[\beta].sub.10]$). Referring to Figure 2, the individual's Y intercept is higher than the grand mean intercept, whereas the individual's slope is shallower than the grand mean slope.

Each individual has his or her own random coefficient $[[\mu].sub.0i]$ and $[[\mu].sub.1i]$ terms. The statistical testing of the variability of the terms is the key difference between multilevel modeling and traditional repeated-measures ANOVA. If statistically significant variability exists in any of the growth parameters (intercepts, slopes, and quadratic terms), a researcher can add predictor variables to the level 2 equations to explain the variability. The ability to use patient-level predictor variables allows multilevel models to explore individual differences.

Using Raudenbush and Bryk's (2002) terminology, a model that describes the variability among growth parameters without predictor variables is called an unconditional model. An unconditional model that adds predictor variables to explain any significant variance in growth parameters is called a conditional model. The authors present a numerical example of unconditional and conditional growth modeling in the next section.

Relationship of the Statistical Model to Clinical Phenomena

The model discussed earlier is a representation of how a sample of patients might change over time with regard to a single sign or symptom. The level 1 model captures the process of change in an individual. What clinicians might see as an absence of a sign or symptom at the start of therapy followed by a rapid development and resolution of erythema for a given patient would be captured as growth parameters for that patient. The parameters would indicate an intercept of zero and a quadratic term that is highly negative (the slope term is less important in a quadratic model than in a linear model). Just as each patient might show a different pattern of rise and fall of erythema, the level 1 parameters (the Y intercept, $[[\pi].sub.0i]$; slope, $[[\pi].sub.1i]$; and

quadratic term, $[\pi]_{.2i}$) would differ. In addition, if the clinical phenomena were known to show a variable expression, a researcher would expect that the measures on individual variability in the statistical model (the $[\mu]$ terms discussed earlier) would show a high degree of variability. Finally, just as a clinician might see that the progression of erythema could differ depending on gender or previous history, the conditional model discussed earlier could test that association. In those ways, the statistical model can be congruent with the clinical picture and can serve as a rigorous test of hypotheses that are developed from clinician experiences or from a biologic model such as that proposed by Sonis (2004a). Thus, with an appreciation of the fundamentals of growth-curve modeling, researchers can formulate questions about changes in signs or symptoms in a more rigorous fashion and develop hypotheses that can be subjected to statistical analyses.

Example of Growth-Curve Modeling Using Oral Mucositis and Pain Data

Parent Study

To illustrate the growth-curve modeling approach to studying change over time, the authors employed individual growth-curve modeling to clinicians' observational ratings of erythema and patients' self-reported ratings of oral pain, the defining components of OM (McGuire et al., 1993). In the parent study (McGuire, Yeager, et al., 1998), a sample of 153 patients received high-dose chemotherapy in preparation for bone marrow or stem cell transplantation ($n = 133$) or for leukemia induction therapy ($n = 20$). Although the study was a randomized clinical trial testing the effects of a psychoeducational intervention for reducing duration and severity of OM and pain, data from the experimental and usual control groups were aggregated for the purposes of this analysis. After patients completed chemotherapy, researchers collected data from patients in their hospital rooms on designated study days (three times per week) in a manner designed to capture developing, peaking, and resolving OM and pain. Trained nurses and a dentist conducted observational ratings of OM (including erythema) using the 20-item Oral Mucositis Index (McGuire et al., 2002). Patients self-reported ratings of oral pain using the Brief Pain Inventory (Cleeland, 1989). The erythema score was computed as the mean of severity of erythema (rated on a scale ranging from 0 [normal] to 3 [severe] across nine sites in the mouth [upper and lower labial mucosa; right and left buccal mucosa; dorsal, lateral, and ventral tongue; floor of the mouth; and soft palate]). Erythema and oral pain scores were similar to total average scores reported in earlier studies (McGuire et al., 1993; Schubert, Williams, Lloid, Donaldson, & Chapko, 1992). The focus here is on erythema as opposed to ulceration because ulceration was less prominent than erythema in the parent study data.

Modeling

The unconditional and conditional growth-curve models were estimated, as recommended by Byrk, Raudenbush, and Congdon (2002). In the process, the researchers estimated a quadratic form of the trajectories of erythema over eight time points that were defined as study days. The quadratic form was chosen because previous reports of OM have indicated this type of trajectory (McGuire et al., 1993; Sonis, 2004a; Woo, Sonis, Monopoli, & Sonis, 1993). Models were conducted with no centering, so the intercept is equivalent to the level of erythema and pain at the beginning of the study, the linear slope indicates the rate of change per unit of time, and the quadratic term indicates the curvature (acceleration or deceleration) of erythema and pain scores.

The first analysis conducted was an unconditional model to inferentially test that the intercept, slope, and quadratic terms were different from zero and to investigate whether the individual differences in the growth parameters had sufficient variability. The second analysis consisted of adding the predictor variable of gender to explain residual variance (variability), thus creating a conditional model. The models' equations with intercept, linear, and quadratic parameters for erythema are shown next. Parameter estimates for both erythema and self-reported OM pain are shown in Table 1.

Table 1. Results for Unconditional and Conditional Growth Models of

Erythema

	Unconditional Model		Conditional Model	
Fixed Effect	Estimate	SE	Estimate	SE
[[beta].sub.00] = intercept	0.0313	0.0275	0.0322	0.0276
[[beta].sub.10] = slope	0.0433 ***	0.0122	0.1158 ***	0.0151
[[beta].sub.20] = quadratic	-0.0065 ***	0.0006	-0.0052 ***	0.0007
[[beta].sub.11] = gender (slope)	--	--	0.0638 **	0.0215
[[beta].sub.21] = gender (quadratic)	--	--	-0.0030 **	0.0010
Random Effect	Variance Component		Variance Component	
[[mu].sub.1i]	[[tau].sub.11] = 0.0150 ***		[[tau].sub.11] = 0.0141 ***	
[[mu].sub.21]	[[tau].sub.22] = 0.0000 ***		[[tau].sub.22] = 0.0000 ***	
[[epsilon].sub.ti]	[[sigma].sup.2] = 0.1678		[[sigma].sup.2] = 0.1682	

* p < 0.05; ** p < 0.01; *** p < 0.001

SE--standard error

Level 1: $[Y_{sub.ti}] = [\pi_{sub.0i}] + [\pi_{sub.1i}] [\alpha_{sub.tl}] + [\pi_{sub.2i}] [\alpha_{sub.tl.sup.2}] + [\epsilon_{sub.tl}]$

Level 2: $[\pi_{sub.0i}] = [\beta_{sub.00}] + [\mu_{sub.0i}]$

$[\pi_{sub.1i}] = [\beta_{sub.10}] + [\mu_{sub.1i}]$

$[\pi_{sub.2i}] = [\beta_{sub.20}] + [\mu_{sub.2i}]$

Unconditional model results: The model for erythema demonstrated no centering of data, which allowed $[\beta_{sub.00}]$ to represent the mean intercept at the beginning of the study. The estimate $[\beta_{sub.00}] = 0.0313$ was not statistically significant from zero (i.e., patients began the study with no erythema on average). $[\beta_{sub.01}]$ was the mean linear rate across time, and the estimate $[\beta_{sub.00}] = 0.1433$ was statistically significant from zero, indicating an increase in erythema at the outset of the study. The estimate $[\beta_{sub.20}] = -0.0065$ was negative and differed significantly from zero, indicating that, on average, subjects' erythema first rose and then declined (recall that the quadratic term is a nonlinear change, which can be seen by the downward curvature of erythema scores in Figure 3). Similar results were obtained with unconditional modeling of self-reported OM pain over time (see Table 2). Thus, in erythema and oral pain, the overall process of change was similar, the intercept was zero, severity increased at the start of the study, and resolution (or partial resolution) occurred as the study progressed.

Table 2. Results for Unconditional and Conditional Growth Models of Self-Reported Oral Pain From Mucositis

Fixed Effect	Unconditional Model		Conditional Model	
	Estimate	SE	Estimate	SE
[[beta].sub.00] = intercept	0.0570	0.0984	0.0586	0.0985
[[beta].sub.10] = slope	0.4193 ***	0.0400	0.6993 ***	0.1165
[[beta].sub.20] = quadratic	-0.0206 ***	0.0020	-0.0349 ***	0.0059
[[beta].sub.11] = gender (slope)	--	--	-0.1780 *	0.0696
[[beta].sub.21] = gender (quadratic)	--	--	0.0091 *	0.0036
Random Effect	Variance Component		Variance Component	
[[mu].sub.1i]	[[tau].sub.11] = 0.1471 ***		[[tau].sub.11] = 0.1403 ***	
[[mu].sub.21]	[[tau].sub.22] = 0.0003 ***		[[tau].sub.22] = 0.0003 ***	
[[epsilon].sub.ti]	[[sigma].sup.2] = 2.1893		[[sigma].sup.2] = 2.1933	

* p < 0.05; ** p < 0.01; *** p < 0.001

SE--standard error

Investigation of the variance components among subjects' linear slope and quadratic random effects (i.e., [T.sub.11] and [T.sub.22]) revealed that both the linear slope and quadratic random effects differed significantly from zero, indicating variability in linear growth rates and quadratic effects among subjects that may be accounted for by additional predictor variables. The nonsignificant random effect of intercept indicates no variability in initial levels of erythema that could be accounted for by predictor variables. Thus, the random effect for intercept was dropped from the unconditional and conditional model. Explaining the significant variance among subjects' growth parameters (e.g., linear slope, quadratic effect) demonstrates how growth modeling better represents individual differences in forms of change over time compared to repeated-measures ANOVA approaches.

Conditional model results: By adding the predictor variable of gender to the unconditional model for erythema and pain, the researchers obtained the following equations.

$$\text{Level 1: } [Y_{.sub.ti}] = [[\pi]_{.sub.0i}] + [[\pi]_{.sub.1i}] [[\alpha]_{.sub.ti}] + [[\pi]_{.sub.2i}] ([[\alpha]_{.sub.ti}^{sup.2}]) + [[\epsilon]_{.sub.ti}]$$

$$\text{Level 2: } [[\pi]_{.sub.0i}] = [[\beta]_{.sub.00}]$$

$$[[\pi]_{.sub.1i}] = [[\beta]_{.sub.10}] + [[\beta]_{.sub.11}] (\text{gender}) + [[\mu]_{.sub.1i}]$$

$$[[\pi].\text{sub}.21] = [[\beta].\text{sub}.20] + [[\beta].\text{sub}.21] (\text{gender}) + [[\mu].\text{sub}.21]$$

For the conditional model, gender was coded as female = 0 and male = 1. Like the unconditional model, no centering of data occurred, which allowed $[[\beta].\text{sub}.00]$ to represent the mean intercept at the beginning of the study. Investigation of the conditional erythema model indicated that, similar to the unconditional model for erythema, the estimate $[[\beta].\text{sub}.00] = 0.0322$ was not statistically significantly different from zero. Interpreting the other growth parameters requires some care. $[[\beta].\text{sub}.10]$ was the mean linear rate across time when gender = 0 (i.e., female), and the estimate $[[\beta].\text{sub}.01] = 0.1158$ was statistically significantly different from zero. The estimate $[[\beta].\text{sub}.20] = -0.0052$ was the average curvature when gender = 0 (female) and was significantly different from zero. $[[\beta].\text{sub}.11] = 0.0638$ was the additional linear slope when gender = 1 (male) and was significantly different from zero. The additional linear slope effect for being male is illustrated in Figure 4, where the males show a faster rise in erythema severity than females. The estimate $[[\beta].\text{sub}.21] = -0.0030$ was the additional quadratic estimate when gender = 1 (male) and was significantly different from zero. The additional quadratic effect for being male also is illustrated in Figure 3, where the males show a sharper decline in erythema severity past the zenith (i.e., more curvature). Investigation of the variance components among subjects' linear slope and quadratic random effects (i.e., $[[\tau].\text{sub}.11]$ and $[[\tau].\text{sub}.22]$) revealed that both the linear slope and quadratic random effects differed significantly from zero, indicating variability in linear growth rates and quadratic effects among subjects that may be accounted for by additional predictor variables besides gender. Self-reported ratings of oral pain showed very similar results; the growth parameters are included in Table 2.

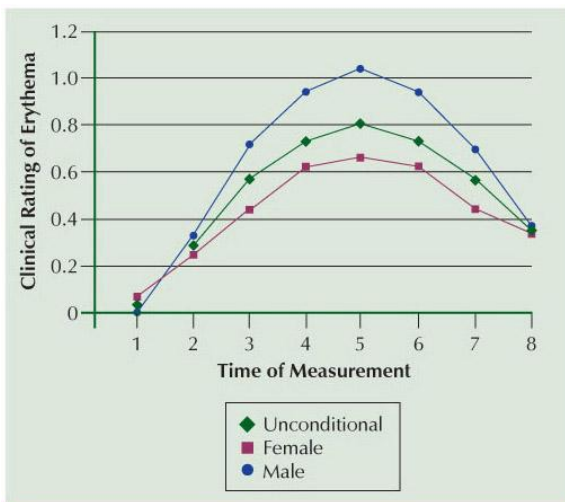


Figure 4. Growth Curves for Conditional Model (Gender) With Unconditional Model Superimposed

Discussion

This article delineates the utility of multilevel growth-curve modeling to the study of change over time. The authors demonstrated that utility by the application of multilevel models to repeated measures of OM (clinician-rated erythema and patient self-reported ratings of oral pain). The results for erythema and pain were consistent with previous reports in the literature (McGuire et al., 1993; Schubert et al., 1992; Sonis, 2004b; Woo et al., 1993). The quadratic models of change also resulted in significant models commensurate with published reports of patterns of OM based on typical mean scores (McGuire et al., 1993; Schubert et al.; Sonis, 2004b; Woo et al.). In addition, the curve parameters of erythema were associated with gender, which also is consistent with reports of factors associated with OM (Avritscher et al., 2004). Another important outcome of the analyses is that the results help support or extend understanding of the pathobiologic model of OM (Sonis, 1998, 2004b), including clinical manifestations, correlates, and risk factors.

This article is the first report, to the authors' knowledge, to examine the utility of multilevel growth-curve analysis in studying changes in OM over a clinical trajectory. Future studies could employ similar methods to test predictions based on the evolving pathobiologic model of OM (Anthony, Bowen, Garden, Hewson, & Sonis, 2006; Sonis, 2007; Sonis et al., 2007; Sonis, 1998, 2004b), with the aim of adding to existing knowledge about this critically important side effect of high-dose chemotherapy. For example, multilevel growth-curve analysis might be used to predict whether individual trajectories of change in erythema and ulceration are related to patient-related (e.g., demographic) or treatment-related (e.g., diagnosis, treatment regimen) variables or to underlying mechanistic processes indicated by biologic measures such as cytokine levels. Thus, this analytic strategy could contribute to an enhanced understanding of pathobiologically based individual variations in the clinical expression of OM.

Another critical advantage of using multilevel growth-curve analysis is that analyses could lead to fuller integration of mechanistic and etiologic models such as Sonis' (2004a) OM model into the broader context of symptom clusters in patients with cancer (Barsevick, 2007; Kim et al., 2005; Lee et al., 2004; Miaskowski & Aouizerat, 2007). For example, the pathobiologic model of mucositis suggests that the complex processes underlying the development of OM also may be implicated in the development of other signs and symptoms that are observed concurrently with mucositis, such as pain, sleeping alterations, fatigue, and emotional distress (Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Lee et al.; McGuire, 2002; McGuire et al., 1993; McGuire, Owen, & Peterson, 1998; Miaskowski & Aouizerat). With increased knowledge of underlying causative mechanisms and new ways to analyze change over time in multiple signs or symptoms, the interrelationships of pathobiology and clinical trajectories may be explored in ways that advance understanding of symptom clusters more rapidly.

Another potential use of this methodology is in the analysis of other symptoms (e.g., fatigue) or combinations of signs and symptoms (e.g., OM, pain, fatigue). It could be an important new approach to analyzing potentially complex relationships among symptoms in patients with cancer. Finally, this method offers useful advantages for current and future work on uncovering processes that underlie the clustering of symptoms, consistent with recommendations by numerous experts (Barsevick, 2007; Barsevick, Whitmer, Nail, Beck, & Dudley, 2006; Kim et al., 2005; National Institutes of Health, 2002). Relevant targets could include proposed models for relationships among symptoms such as Lee et al.'s (2004) cytokine model and Parker, Kimble, Dunbar, and Clark's (2005) symptom interactional framework.

Limitations

As with any research, the results presented herein have some inherent limitations. First, they reflect a secondary data analysis from a study testing the effects of a psychoeducational intervention in reducing the duration and severity of OM and oral pain in patients receiving high-dose chemotherapy, so the data were analyzed for different purposes than intended in the original study. Second, considerable data were missing beginning at about 14 days after initiation of chemotherapy because of patient discharges from the hospital, which limited the researchers' ability to apply the growth-curve techniques across the full trajectory of signs and symptoms. Substantive studies may require the use of sensitivity analyses to control for biases resulting from data that are not missing at random (Diggle & Kenward, 1994; Troxel, Harrington, & Lipsitz, 1998).

Conclusion

This article illustrates the potential utility of multilevel growth-curve modeling techniques in the study of change in signs and symptoms over time. The results relative to the analysis of erythema are consistent with previously published studies and extend the modeling by delineating several patterns obscured by traditional analyses of mean scores. Knowledge of these patterns may help clinicians approach assessment differentially, depending on treatment and other factors. The multilevel growth-curve modeling technique appears to be well suited to complex modeling of multiple signs or symptoms and related outcomes. The method may enhance the

ability of researchers to analyze results of the complex data that emerge when symptom clusters are being studied. The data include the process of change in clinical signs and symptoms and the relationship of such processes to other individual and clinical characteristics of patients, as well as to underlying mechanistic models.

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