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The crossover design to evaluate the efficacy of plaque removal in tooth-brushing studies

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Abstract

Objectives: To evaluate the crossover clinical trial design to assess plaque removal efficacy of the Sonicare Elite.

Material and Methods: A single-cohort, 12-week, two-treatment, single-blind, crossover clinical trial recruited 45 subjects. Plaque was recorded using the modified Quigley and Hein index plaque index (PI). After screening, subjects used the toothbrush for 2 weeks and were reminded to abstain from tooth cleaning 12–18 h prior to appointments. At visit two, subjects were randomized to 2 or $2\frac{1}{2}$ min. brushing time. PIs was recorded pre- and post-brushing. Subjects brushed for the allocated time for a further 2 weeks. At visit 3, PIs were recorded pre- and post-brushing. Two weeks later, at visit 4, the subjects crossed over and the protocol was repeated.

Results: There was no evidence of a learning effect within each arm of the crossover. A significant period effect was detected; however, no significant treatment by period effect was found. $2\frac{1}{2}$ min. brushing removed more plaque at full mouth ($p = 0.037$), smooth ($p = 0.012$) and lingual ($p = 0.002$) sites compared with 2 min.

Conclusion: The crossover design is a valid model for assessing plaque removal efficacy in tooth-brushing studies where no carry-over effect is clinically plausible.

Key words: plaque removal; powered toothbrushes; trial design

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There is considerable variation in the design of clinical trials to evaluate the efficacy of plaque removal in tooth-brushing studies and this problem has been highlighted in a systematic review, which concluded that observation of methodological guidelines and greater standardization of design would benefit future trials and meta-analyses (Heanue et al. 2003). In an earlier review (Heasman & McCracken 1999), we established that the vast majority of powered toothbrush studies were of parallel group design although a number of researchers have utilized split-mouth, crossover designs to compare manual with powered brushes (Walsh & Glenwright 1984, Quirynen et al. 1994) and different models of powered devices (Van der Weijden et al. 1993a, b, 1994).

There are a number of advantages in using crossover designs in clinical trials: for example, the patients or subjects act as their own controls. The primary strength of crossover trials is, therefore, an increase in efficiency and precision, and because within-subject variability is often less than between-subject variability, the sample size is usually lower than for comparable parallel group designs (Piantadosi 1997). Conversely, there are well-recognized disadvantages of crossover trials: carry-over effects; treatment by period interactions; the effect of drop-outs on the analysis; and the potentially more complex statistical analysis is required to ensure that carry-over effects have not confounded the estimates of treatment effect.

In a clinical trial to compare the efficacy of two powered toothbrushes, we previously used a crossover design to demonstrate superiority of one brush over the other (McCracken et al. 2004). This observation led us to further investigate the potential value of the crossover design, but in the current study the variable (treatment) under investigation was tooth-brushing time rather than the toothbrush itself.

Material and Methods

This was a single cohort, 12-week, two-treatment, single-blind, crossover clinical trial to compare the plaque removing efficacy of a powered toothbrush using different brushing times. A favourable ethical opinion was obtained from the Local NHS Research Ethics Committee of Newcastle upon Tyne, UK.

Subjects

Forty-five subjects were recruited to the study. Inclusion criteria stipulated that

subjects should be 18–65 years of age, have a minimum of 18 natural teeth, be in excellent general health and have an overnight, pre-brushing mean plaque index (PI) of at least 1.8 recorded at the screening visit. The exclusion criteria have been published previously (McCracken et al. 2002).

All subjects provided written, informed consent to participation at the screening visit and the trial was undertaken with consideration of ICH GCP guidelines.

Power and sample size

The power calculation was performed using data from both internal and published parallel group studies. With $n = 45$, there was 75% power to detect a difference of 5% (or greater) plaque score reduction between two parallel groups (treatments), assuming a standard deviation of 8–12, at the 0.05 level of significance. The difference of 5% had been observed repeatedly in internal, pilot studies.

Randomization

The subjects were randomized to a treatment sequence for tooth-brushing times 2 min. then $2\frac{1}{2}$ min. or $2\frac{1}{2}$ min. then 2 min. within blocks of eight or approximately the number of subjects evaluated on one day of the trial, using a computer-generated randomization schedule.

Calibration of the examiner

Prior to the study, the examiner (P. A. H.) was calibrated for accuracy and repeatability using the Turesky modification of the Quigley and Hein PI (Turesky et al. 1970) on a population of five subjects identical to those selected for the study. Calibration training preceded the calibration exercise proper. The intra-examiner κ statistic was 0.63 with 77% perfect agreement and $99 \pm 1\%$ agreement scores measured on 504 posterior sites. In the main study, the examiner was blinded at all times to the treatment intervention provided.

Powered toothbrush

The toothbrush model that was used by subjects for the entire duration of the study was the Sonicare Elite (Philips Oral Healthcare, Snoqualmie, WA, USA).

Plaque scoring

Plaque was scored after disclosing at six sites per tooth (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual) using the Turesky et al. (1970) modification of the Quigley and Hein PI (1962) (Quigley & Hein 1962, Turesky et al. 1970). Plaque was scored on all teeth present with the exception of the third permanent molars. All measurements were recorded by a single, experienced, calibrated examiner (P. A. H.).

Study design

The clinical trial was carried out over five visits. These were preceded by a study information meeting at which the information document was presented and the subjects had an opportunity to ask questions about the study. Specific ethical issues such as the requirement to abstain from tooth cleaning prior to study visits were addressed.

Visit 1 – screening

Subjects were instructed not to brush their teeth or use oral hygiene aids for 12–18 h prior to this visit. When a subject met the inclusion criteria the test teeth were disclosed and the PI recorded. The minimum entry PI of 1.8 was confirmed. Those subjects who qualified and agreed to take part were given a Sonicare Elite toothbrush to use at home for 2 weeks as part of a familiarisation period to become accustomed to the toothbrush. The manufacturer's written instructions for the toothbrushes were given to the subjects and these were read under supervision so that any queries could be answered directly. The subjects were instructed to brush for 2 min. on two occasions each day. The subjects were reminded not to brush their teeth for 12–18 h prior to visit 2. All brushing events throughout the study were undertaken using a pea-sized amount of the same dentifrice (Colgate Total, Colgate Palmolive (UK) Ltd. Surrey, UK).

Visit 2 (2 weeks [± 2 days] after screening)

Subjects were assigned to their tooth-brushing times (2 *versus* $2\frac{1}{2}$ min.) according to the randomization chart. PI was recorded before and after brushing. The subjects were instructed to brush for 30 s in each of the four quadrants and, for those subjects randomized to the $2\frac{1}{2}$ min. brushing group, an additional 30 s on the lingual surfaces of the lower teeth. The subjects were reminded that the quadpacer feature of the toothbrush has a short beep and a pause in the brushing action at 30, 60 and 90 s of actual brushing time, signalling the subject to move to the next quadrant. The subjects were also reminded that the brush should be switched off (for not more than 20 s) when not in use if they wished to pause to expectorate excess toothpaste slurry or to wet the brush. For those subjects assigned to the $2\frac{1}{2}$ min. brushing time, the quadpacer feature was programmed to operate for the full tooth-brushing duration. The subjects were reminded not to brush their teeth for 12–18 h prior to visit 3.

Visit 3 (2 weeks [± 2 days] after visit 2)

After checking compliance, PI was again recorded before and after the same tooth-brushing event carried out in visit 2 (2 or $2\frac{1}{2}$ min.). All subjects were then asked to brush with the Sonicare Elite for 2 min. for the following 2 weeks, which comprised the wash-out period for the cross-over. Subjects were reminded not to brush their teeth for 12–18 h prior to visit 4, which was scheduled for 2 weeks (± 2 days) after visit 3.

Visits 4 (2 weeks [± 2 days] after visit 3) and 5 (2 weeks [± 2 days] after visit 4)

At visit 4, the subjects were assigned to the second sequence of the study according to the randomization chart. The sequence of protocol events at visits 4 and 5 was identical to that undertaken at visits 2 and 3. On completion of visit 4, subjects were reminded to abstain from oral hygiene measures for the 12–18 h period prior to visit 5. On completion of visit 5 the subjects were considered to have completed the trial.

Safety and adverse events

Adverse events were recorded and a clinical examination for soft tissue lesions was undertaken at every time point in the study.

Data collection

All data were collected on electronic data entry forms. Scanned data were reviewed and verified for completeness and accuracy.

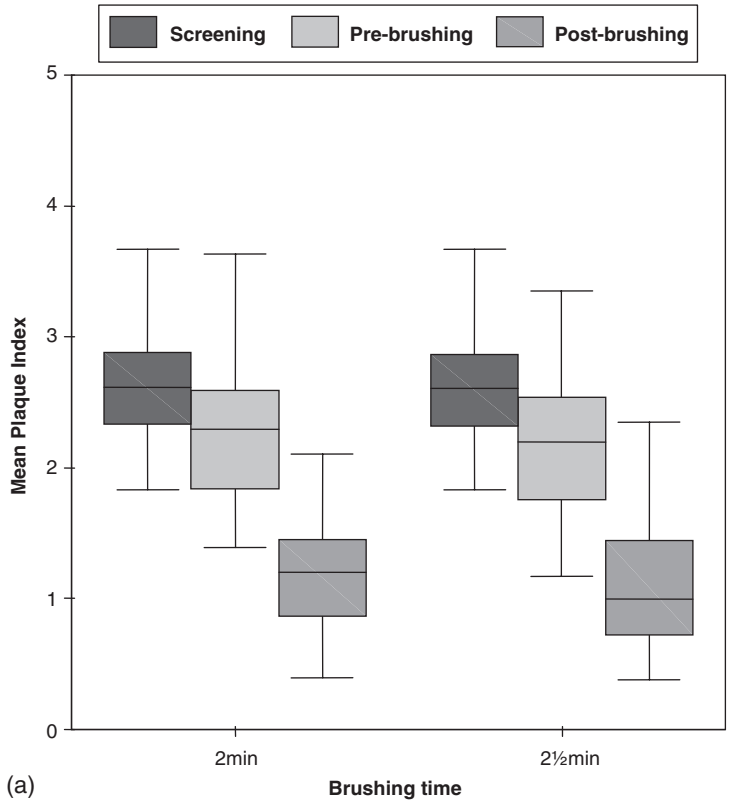

Fig. 1. (a) Box and whisker plots of the combined visit data showing the pre- and post-brushing mean plaque indices (PIs) for the two brushing times for all surfaces. Screening PIs are also shown. The plots show the median scores, quartiles and the limits of distribution. (b) Box and whisker plots of the combined visit data showing pre- and post-brushing plaque scores for the two brushing times for lower lingual surfaces. Screening plaque scores are also shown. The plots show the median scores, quartiles and the limits of distribution.

Statistical analysis

The basic design is a two-period crossover study with two replications. Period 1 comprised visits 2 and 3; period 2 comprised visits 4 and 5 with each subject receiving a different treatment (brushing time) in period 1 from that received in period 2. Visits 2 and 4 can be considered as a first replication of the basic crossover design and visits 3 and 5 as a second. The following analytic strategy was adopted with all analyses undertaken using SPSS software.

(a) Estimating the effect of brushing for an additional 30 s:

Plaque scores for all surfaces, smooth surfaces and lower lingual surfaces were analysed separately using analysis of variance with variation between subjects, periods and replications included as fixed effects.

(b) Evaluating the different components of the crossover design

Initially we analysed final lower lingual plaque scores from the first replication (visits 2 and 4) using only analysis of variance with subjects, period and treatment included as fixed effects. This corresponds to the simplest possible crossover design.

To assess the benefits of collecting baseline data we then included pre-brushing scores at visits 2 and 4 as a covariate. The estimated 95% confidence interval (CI) for the difference between the two brushing times was compared with that obtained from the previous model.

To assess the benefits of the additional replication, data from visits 3 and 5 were then included. Replication was included as an additional fixed effect (this effect can be considered as the difference between the mean plaque scores from visits 2 and 4 and the mean plaque scores from visits 3 and 5). The analysis of variance model was fitted with and without baseline plaque as a covariate. Again the CIs for the treatment effect were compared with those from previous models.

When analysing a crossover design Chilton & Fleiss (1986) recommended that the possibility of a carry-over effect must be considered. To do this within an analysis of variance framework it is necessary to fit variation between subjects

as a random effect and then fit a period by treatment interaction. Although a carry-over effect in this study was not felt to be plausible, this was done for purposes of illustration – first using only data from visits 2 and 4 and then data from all visits.

Results

The number of subjects who attended the visits as follows: screening (visit 1) – 45; visit 2 – 44; visit 3 – 42; visit 4 – 44; visit 5 – 43.

The incidence of adverse events in the trial was low. Thirteen events were reported in nine subjects. The events comprised tooth sensitivity, delayed healing of an extraction socket, ulcers of the soft tissues (tongue, buccal mucosa, oral mucosa), pericoronitis and sore gingiva. Of the 13 events, six were possibly and one event of tooth sensitivity was definitely related to the study intervention. None required remedial treatment other than application of a desensitizing varnish to sensitive teeth. All symptoms resolved by the end of the trial.

Table 1. The main effects analysis of the differences in mean plaque index (pre- to post-brushing) between tooth-brushing times with the Sonicare Elite toothbrush for period, visit and time effects

	Brushing time effect	
Sites	Difference	CI
Full mouth	-0.1^{*}	$-0.115,\ -0.004$
Interproximal	-0.1	$-0.124,\ -0.005$
Smooth	-0.1^{**}	$-0.114,\ -0.015$
Lower lingual	-0.2^{***}	$-0.302,\ -0.072$

$^{*}p = 0.04$, $^{**}p < 0.01$, $^{***}p = 0.002$.
CI, confidence interval.

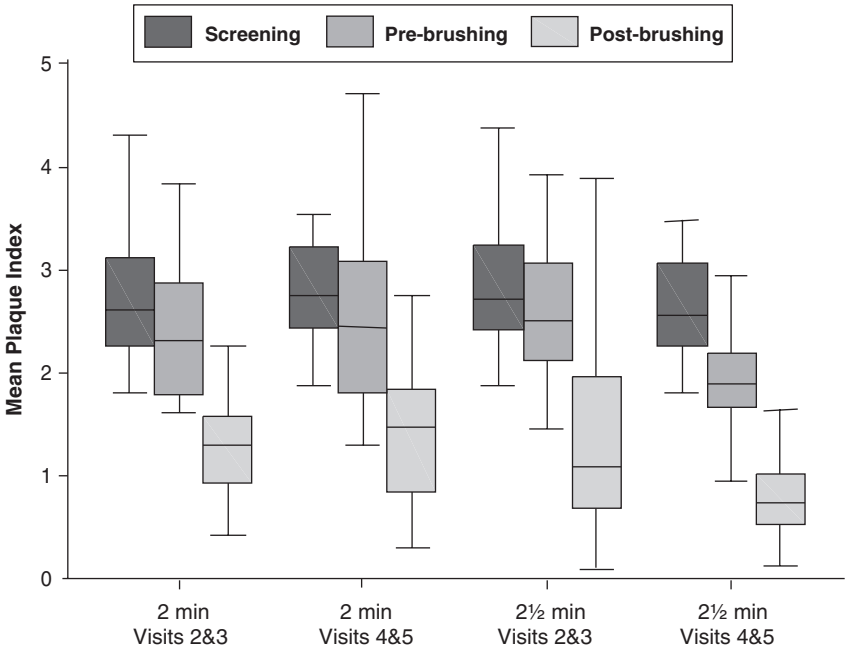

Fig. 2. Box and whisker plots showing screening, pre- and post-brushing groups mean plaque indices at lower lingual sites for each visit and each brushing time. The plots show the median scores, quartiles and the limits of distribution.

The combined visit mean pre- and post-brushing PIs for all surfaces by brushing time and including screening data are presented diagrammatically as box and whisker plots in Fig. 1a. Pre- and post-brushing mean PIs for the lingual surfaces only and again including screening data are presented diagrammatically as box and whisker plots in Fig. 1b. The mean magnitudes of the differences between the interventions (brushing times) together with significance levels and CIs are shown in Table 1.

Subjects removed significantly more plaque when measured at full mouth ($p = 0.04$), smooth ($p = 0.01$) and lower lingual surfaces ($p = 0.002$) when the brushing time was $2\frac{1}{2}$ min. compared with 2 min. (Figs 1a, b, Table 1). Considering the interproximal sites, lower PIs were observed after brushing for $2\frac{1}{2}$ min. but the difference was not statistically significant ($p = 0.07$).

Figure 2 shows data from lower lingual sites only and Table 2 shows the analysis undertaken with the assumption that no carry-over effect was plausible. Parameter estimates with 95% CIs are shown as an estimate of any treatment effect in terms of difference in PI. When using only data from visits 2 and 4 (first replication), the difference between groups was estimated at -0.30 (95% CI: $-0.44,\ -0.16$). Using the data from both replicates and with pre-brushing plaque levels included as a covariable a treatment effect was estimated in favour of the extra 30 s brushing of

Table 2. The effect of adding each element of mean plaque index (PI) data recorded to the analysis of variance

Fixed effects	Replication of data			
	first		second	
	final plaque only	baseline plaque as covariate	final plaque only	baseline plaque as covariate
Period	$-0.17\ (-0.31,\ -0.02)$	$-0.07\ (-0.23,\ 0.10)$	$-0.24\ (-0.36\ -0.12)$	$-0.13\ (-0.26,\ -0.00)$
Replication	NA	NA	$0.04\ (-0.08,\ 0.16)$	$0.07\ (-0.04,\ 0.19)$
Treatment	$-0.29\ (-0.44,\ -0.15)$	$-0.30\ (-0.44,\ -0.16)$	$-0.24\ (-0.37,\ -0.12)$	$-0.20\ (-0.32,\ 10.08)$

Data shown represent the precision of the estimate of differences in mean PI (2 min versus $2\frac{1}{2}$ min. brushing) at lower lingual sites only.

Table 3. The analysis of potential treatment by period interactions upon the differences in mean plaque index by using data from the first replication of the crossover design at lower lingual sites only

Fixed effects	Including baseline plaque as a co-variate?			
	no		yes	
	subjects as a fixed effect	subjects as a random effect	subjects as a fixed effect	subjects as a random effect
Period*	−0.17 (−0.31, −0.02)	−0.17 (−0.31, −0.03)	−0.07 (−0.23, 0.10)	−0.02 (−0.16, 0.11)
Treatment	−0.29 (−0.44, −0.15)	−0.29 (−0.43, −0.15)	−0.30 (−0.44, −0.16)	−0.30 (−0.43, −0.17)
Treatment × period interaction		−0.52 (−1.13, 0.09)		−0.18 (−0.66, 0.29)

*Estimates of effect based on the main effects model including subjects, period effect and treatment effect.

Table 4. The analysis of potential treatment by period interaction upon the differences in mean plaque index using data from both replications of the crossover design at lower lingual sites only

Fixed effects	Including baseline plaque as a co-variate?			
	no		yes	
	subjects as fixed effect	subjects as random effect	subjects as fixed effect	subjects as random effect
Period*	−0.24 (−0.36 −0.12)	−0.24 (−0.36, 0.12)	−0.13 (−0.26, −0.00)	−0.07 (−0.19, 0.05)
Replication*	0.04 (−0.08, 0.16)	0.04 (−0.08, 0.16)	0.07 (−0.04, 0.19)	0.09 (−0.02, 0.21)
Treatment*	−0.24 (−0.37, −0.12)	−0.24 (−0.36, −0.13)	−0.20 (−0.32, −0.08)	−0.18 (−0.29, −0.06)
Treatment period interaction		−0.70 (−1.35, −0.05)		−0.29 (−0.70, 0.13)

*Estimates of effect based on main effects model including subjects, period effect, replication effect and treatment effect.

−0.20 PI units (95% CI: −0.32, −0.08).

Tables 3 and 4 show the results of data from lower lingual sites with examination of any treatment by period interaction that might have arisen from a carry-over effect. Table 3 shows the analysis using only data from visits 2 and 4 and estimates the difference between groups as −0.30 (95% CI: −0.43, −0.17). Table 4 uses both data sets (visits 2, 3, and visits 4, 5) and estimates the difference as −0.18 (95% CI: −0.29, −0.06). Tables 3 and 4 also show the level of treatment by period interaction. When pre-brushing PI was not used as a co-variate, and both sets of data were used, there appeared to be a significant carry-over effect −0.70 (95% CI: −1.35, −0.05). But when pre-brushing PI was used as a co-variate, this effect was substantially reduced with the 95% CI crossing zero.

Discussion

Our group has previously reported models for testing the efficacy of powered toothbrushes in clinical trials (Heasman & McCracken 1999) and these have been applied successfully to short-term studies of prototype toothbrushes for periods of up to 12 weeks (McCracken et al. 2000, 2002). The aim of this study was to investigate data collection within a crossover design of clinical trial using efficacy of plaque removal as the primary outcome measure.

The trial was not typical of many studies (e.g. drug studies) that use the crossover design and, in view of this, a number of the more common problems with crossover designs were not encountered. Firstly, the trial used what is effectively an in vivo, plaque removal model with healthy subjects. The study was designed to investigate the ability to remove plaque using specified tooth-brushing times and was, therefore, assessing adaptation to a behaviour rather than assessing an intervention. There was no disease present that might have resolved (or worsened) during the study, and thus may have contributed to there being different baseline status at the beginning of each period of the crossover. One of the significant limitations of the crossover design occurs in situations when one or both treatments are likely to lead to a resolution of a disease in a short period of time.

Secondly, one potential problem with the classic AB/BA design is the potential effect of ''carry over'' from one treatment period to the next. For this reason, ''wash-out'' periods are incorporated between the treatment arms, and in this study, a 2-week period was chosen to enable the subjects to ''unlearn'' an adapted tooth-brushing behaviour that will have become associated with a prescribed tooth-brushing time. A period effect was noted, however, which, with respect to plaque removal, was in favour of there being less plaque on tooth surfaces during the second period compared with the first. This may have been expected, as subjects would have become more accomplished at using the toothbrush under trial conditions during period 2 compared with period 1. Nevertheless, there was no evidence of a period × treatment interaction, confirming that the advantageous effect of the additional 30 s brushing time was constant in both periods of the trial. Nor was there any evidence of a significant ''learning effect'' within each arm of the study, thus suggesting that the ability to remove plaque for each brushing time was the same at the end as it was at the beginning of each 2-week period.

With respect to the primary outcome of the trial, brushing for $2\frac{1}{2}$ min. effected better plaque removal than did brushing for 2 min. The effect, which was clearly expected, was highly significant ($p < 0.002$) at the lower lingual surfaces that were the target for the additional 30 s brushing time. The effect was not statistically significant at interproximal sites ($p = 0.07$).

The crossover design model is, therefore, with adequate power and sample size, able to detect small and statistically significant differences in plaque

removal using one toothbrush with different brushing times. With baseline plaque included as a co-variate, there were no carry-over or learning effects, although this may not be the case were this model to be used, for example, to test different types of toothbrush. In this study brushing time was used as the principal clinical variable and the magnitude of the statistically significant differences was in the range of 0.1–0.2 units of the mean Quigley and Hein PI (Table 1). The clinical relevance or meaning of statistically significant differences of this order remains questionable and this would be the case irrespective of the type of design used – parallel group or crossover. We recommend, therefore, that a threshold for clinical relevance is set a priori rather than retrospectively following data analysis and that this is particularly important when the relative efficacy of different products is tested either within, or on behalf of the commercial sector.

Finally, it would be inappropriate to extrapolate the results of this study to make any assumptions regarding toothbrushing efficacy in the general population. This trial has used a model with a minimum PI of 1.8 as an inclusion criterion. This is not likely to be representative of a wider cohort of subjects and was used simply to ensure that all subjects had sufficient pre-brushing plaque deposits present to allow a measurable pre- to post-brushing change on each visit during the crossover.

Conclusion

The crossover design for clinical trials appears to be valid and effective in studies evaluating plaque removal using healthy subjects. Analysis of the data must investigate between-visit, period and period × treatment interaction effects, although in the current trial, the absence of the latter helped to justify the validity of choosing this design.

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Clinical Relevance

Rationale for the study: The crossover clinical trial design is an alternative to the parallel arm design, although a recognized disadvantage is the potential for carry-over effects.

Principal findings: The design detected small differences between the chosen interventions. With the inclusion of a pre-brushing PI as a co-variate, the period by treatment interaction was minimal.

Practical implications: The crossover design is a valid model for plaque removal studies, but period by treatment interactions must be explored.