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Serial controlled N-of-1 trials of topical vitamin E as prophylaxis for chemotherapy-induced oral mucositis in paediatric patients

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ABSTRACT

The objectives were (1) to determine whether in children undergoing doxorubicin-containing chemotherapy, topical vitamin E decreases an objective measurement of oral mucositis compared to placebo, and (2) to assess the feasibility of an innovative trial design in paediatric cancer, combining N-of-1 trials using Bayesian meta-analysis. We conducted a series of N-of-1, double-blinded, randomised controlled trials in children ⩾ 6 years of age receiving repeated cycles of identical doxorubicin-containing chemotherapy. Each study cycle was followed by topical vitamin E (800 mg) or placebo.

We enroled 16 children and 45 post chemotherapy cycles were randomised to vitamin E (N = 22) or placebo (N = 23). There was no difference in objective mucositis scores with a mean score of 0.2 with vitamin E and 0.3 with placebo. Topical vitamin E does not reduce doxorubicin-induced oral mucositis in children. The use of N-of-1 studies and Bayesian meta-analysis may facilitate the study of some therapies in paediatric oncology.

1. Introduction

Oral mucositis is a common consequence of chemotherapy, occurring in approximately 40% of standard-dose chemotherapy regimens.[1] It is an important sequela of cancer therapy because it is painful and affects quality of life, may lead to hospitalisation for hydration or pain control, and provides a portal of entry for oral microflora. In addition, oral mucositis has become a major dose-limiting toxicity and consequently, may limit the delivery of anti-cancer therapy.[2]

There are no feasible therapies that can prevent oral mucositis in children.[3] Vitamin E is a fat-soluble essential

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vitamin that may protect against doxorubicin-induced oral mucositis through its anti-oxidant properties.[4,5] In a mouse model of toxic gastrointestinal mucositis, vitamin E was able to prevent doxorubicin-induced mucositis and improve survival.[6] In a randomised controlled trial of 10 adults undergoing induction chemotherapy for acute myelogenous leukaemia, prophylactic topical vitamin E reduced the proportion of days with severe mucositis (grade 3 or 4) from 42/60 days in the placebo group to 20/90 days in the vitamin E group ($P < .001$ using the Chi square test).[7] In addition, topical vitamin E may be effective when used to treat doxorubicin-induced oral mucositis. In a randomised controlled trial of 18 adults undergoing chemotherapy, those randomised to receive topical vitamin E had more rapid resolution of mucositis compared with placebo. In this study, 6/9 vitamin E patients had complete resolution of their lesions within 4 days of initiating therapy, whereas 8/9 patients receiving placebo did not have complete resolution of lesions during the study period of 5 days ($P = 0.025$).[8]

In this study, we examined the efficacy of topical vitamin E as prophylaxis against chemotherapy-induced mucositis in children with a novel methodology appropriate for the study of rare conditions, namely combining *N*-of-1 trials using Bayesian meta-analysis.[9] This design may be advantageous in uncommon conditions because the *N*-of-1 methodology allows precise estimation of a within-subject treatment effect, while the Bayesian analysis affords great flexibility with the ability to continually update the data, and provides a direct estimate of the probability of treatment efficacy.[10]

Our objectives were (1) to determine whether in children undergoing doxorubicin-containing chemotherapy, topical vitamin E decreases an objective measurement of oral mucositis compared to placebo and (2) to assess the feasibility of an innovative trial design of combining *N*-of-1 trials using Bayesian meta-analysis.

2. Patients and methods

2.1. Patients

Children were included if (1) they were diagnosed with cancer and treated at the Hospital for Sick Children, Toronto, Canada; (2) their planned chemotherapy included at least two identical courses of doxorubicin-containing chemotherapy in which the dose of doxorubicin was at least 60 mg/m^2 per course; (3) they were at least 6 years of age and less than 18 years at the time of study enrolment; and (4) they lived in the Greater Toronto area. We excluded those with an allergy to vitamin E or placebo, those developmentally unable to comply with topical vitamin E application and those receiving head or neck irradiation.

2.2. Study design

This study was a randomised, controlled double-blinded study, which used an *N*-of-1 design and Bayesian analysis (see below for details). The study was approved by the Research Ethics Board at the Hospital for Sick Children and written informed consent from the patient and/or guardian and child assent were obtained upon enrolment to the study. At enrolment, baseline characteristics were recorded and then, the subject underwent an *N*-of-1 study. For each subject, the number of identical, eligible doxorubicin-containing cycles was noted and grouped into treatment sets consisting of two consecutive cycles. Each child had 1–3 treatment sets consisting of 2–6 doxorubicin-containing chemotherapy cycles. Vitamin E and placebo then were randomly allocated within each treatment set. Randomisation was performed by computer allocation and the sequence remained concealed to all members of the research team and to those participating in clinical care until the conclusion of the study. The randomisation sequence was maintained in the pharmacy at The Hospital for Sick Children. Randomisation was performed in blocks of four within an individual. The family, health care workers, and study team were blinded to the assignment throughout the intervention and follow-up periods, and every assessment of outcomes was performed with the study team blinded to allocation.

The study medication began 24 h after the completion of doxorubicin chemotherapy and 2 mL was administered once daily for 2 weeks. The vitamin E solution contained 800 mg (DL-α-tocopheryl acetate) per dose and was diluted with corn oil (Hoffman LaRoche). The placebo solution consisted of an identical volume of the carrier solution for the vitamin E dilution (corn oil) and was indistinguishable in terms of color, smell and taste from the vitamin E solution. The subject was asked to swish the study medication around the mouth for at least 30 s prior to spitting the medication out. The subject was instructed to refrain from rinsing the mouth or from eating or drinking for a minimum of 30 min after study medication application. Typically, study medication was administered at home as children usually were discharged following the completion of chemotherapy.

Because concurrent herpes simplex virus infection potentially could cause a biased estimate of the within-subject treatment effect, we obtained an oral swab for herpes simplex virus polymerase chain reaction (PCR) at day 10 or 14 of each cycle.[11]

2.3. Outcome measures

The primary outcome measure was an objective mucositis assessment performed by two trained research assistants according to a reliable and valid scale developed by Sonis et al.[12] Each child was assessed by only one of these two research assistants throughout that child's participation period. The objective mucositis scale assesses erythema and ulceration on a scale of 0–5 at each of 9 intra-oral sites and these assessments are averaged to result in an overall mucositis score ranging from 0 (no mucositis) to 5 (worst score possible). The objective assessments were obtained on days 7, 10, 14 and 17 of each study cycle. Most assessments occurred at the participants' homes although some were performed in hospital during clinic visits or if the child was hospitalised (such as for febrile neutropenia). A one-day deviation from the schedule in ascertainment of each score was permitted in order to reduce the need for visits on the weekend and in order to allow assessment to be performed during regularly scheduled clinic visits.

Prior to beginning the study, each assessor was trained to conduct objective mucositis assessments by a paediatric dentistry (PD). Inter-rater reliability was assessed using 4 patients with a mean mucositis score of 0.5 (range 0, 1.56); the intraclass correlation coefficient was 0.99 (95% CI 0.83, 1.00) indicating excellent reliability.

The secondary outcome measures included two subjective assessments of mucositis, which were recorded from days 5 to 20 after chemotherapy, and some measures related to other medical care required during the trial. One set of subjective measures consisted of visual analogue scale (VAS) scores for pain and difficulty swallowing; the horizontal 10 cm VAS was anchored at 0 (no symptoms) and 10 (worst symptoms possible). A second subjective measure was the World Health Organization (WHO) mucositis scale that is based upon the ability to eat and drink.[13] The WHO mucositis score ranges from 0 (no symptoms) to 4 (cannot swallow even water). These assessments were recorded in a diary by the participant or the participant's parent. Other secondary outcomes were the number of cycles in which the subject received opioid analgesia, the average amount of opioid analgesia administered per kilogram, the number of doses of topical analgesia received, and the number of cycles in which intravenous hydration and parenteral nutrition were administered. We also examined the proportion of cycles in which febrile neutropenia and bacteremia were documented, the proportion of days patients were compliant with the study medication, and any unexpected toxicity.

Successful accrual of our planned sample size, completion of the study and ability to analyse our collected data was considered to be evidence of the feasibility of combining *N*-of-1 studies using Bayesian meta-analytic techniques in the paediatric cancer supportive care setting.

2.4. *Statistical methods*

The statistical methods used were a variation on the approach described by Zucker, which assumed conditional Gaussian distributions for observed outcomes.[9] For our analysis of the primary outcome (objective mucositis scores) and the subjective mucositis scores, because our data were highly skewed, we assumed that the scores followed a gamma distribution.[14] We assumed that there was a common shape parameter for all observations and a subject-specific scale parameter. With this type of regression model, treatment effects and subject-to-subject random effects are on the multiplicative scale. The model also accounted for the repeated nature of the data; however, the specific modeling was different depending on the number of assessments performed. For the objective measure in which assessments occurred four times per cycle, assessment day was adjusted as a categorical variable. In contrast, for subjective scores, because there were 16 observations per cycle, we modelled the effect for observation day as a quadratic regression, which allows for a common pattern of scores over time – increasing then decreasing. The effect of vitamin E at any particular time for any particular subject was expressed as a ratio of means (vitamin E score: placebo score), which was the exponential of the treatment effect coefficient in the regression equation. Therefore, since high scores are associated with worse mucositis, a ratio of means less than one suggests that vitamin E is associated with less mucositis. We present the mean treatment effect and its 95% credible region (CR); these were calculated as the corresponding percentiles from the posterior distribution.

Compliance was assessed using a random effects logistic regression, with subject-specific random effects for the log-odds of compliance in the placebo period and for the log-odds ratio for compliance in the vitamin E period. For each cycle, and conditional on these subject-specific random effects, the number of days of compliance was treated as a binomial outcome with sample size 14. A similar approach was used to model opioid analgesia use, except that the outcome was receipt or non-receipt during each cycle and a fixed effect was used for the log-odds ratio relating vitamin E to use of opioid analgesia.

For each Bayesian regression, we used non-informative priors, which allow the results to be driven by the data. The prior distribution for the coefficient for treatment effect (log of the ratio of means) was assumed to be normal with a mean value of 0 (ratio of means = 1); however, we chose the variance of this parameter (log of the ratio of means) such that there was a 95% prior probability that the ratio of means due to treatment was between 0.1 and 10 (clinically reasonable extremes). We also performed analyses with different prior distributions for the coefficient for the treatment effect to assess how sensitive the results were to these different priors and to demonstrate how the results would be interpreted by people with different prior convictions about the effectiveness of vitamin E for preventing mucositis. We repeated the analysis using a sceptical prior; this expresses scepticism that an association exists between the treatment and outcome. The sceptical prior was centred at a ratio of means of 1, but the variance was chosen such that there was a 95% prior probability that the ratio of means was between 0.5 and 2. We also repeated the analysis using an optimistic prior distribution for the treatment effect centred at the predefined clinically important value of 0.8 and with 95% prior probability on the range 0.6–1.07. We used diffuse priors for the shape of the gamma distribution (exponential [1]), and the common intercept (normal [mean = 0, variance = 10^6]).

We decided to enrol 16 participants based upon the number of eligible patients we thought could be accrued within a reasonable time frame of 2–3 years. We had decided *a priori* that evidence of vitamin E efficacy would be demonstrated if there was at least a 95% probability that vitamin E was associated with less mucositis (i.e. the ratio of means was <1). We also present the probability that vitamin E decreased mucositis by a clinically relevant amount, which we considered *a priori* as at least a 20% reduction in mucositis (i.e. the ratio of means was less than 0.8).

The Bayesian analysis was performed using WinBUGS version 1.4 in which Markov Chain Monte Carlo (MCMC) with Gibbs Sampling is used to make inferences. After a burn-in of 10,000 updates, 20,000 iterations were performed. We ran three parallel MCMC chains and assessed convergence using the Gelman–Rubin statistic. The model fit was assessed using a posterior predictive check based on pseudo-replicate data and found to be more than adequate. Appendix 1 provides details of the models. Code used for the analysis of objective

outcomes is available at http://fisher.utstat.toronto.edu/georget/LillianSung/MucositisIndex.html. We used published guidelines to aid in the reporting of the results of this Bayesian analysis.[15]

3. Results

Between June 2001 and August 2004, 22 children were eligible to participate in this study. Six families refused to participate and thus 16 children were enroled during the study time period.

The 16 children had a median age of 12.7 years (range 6.4–15.1 years) at cancer diagnosis and 10 (63%) were male. The most common diagnosis was Ewing's sarcoma/peripheral primitive neuroectodermal tumour in 9 (56%) followed by large cell lymphoma in 3 (19%) and osteosarcoma in 3 (19%). One child had relapsed embryonal rhabdomyosarcoma. Four children had two planned cycles of doxorubicin, while the other 12 had four or more planned cycles of doxorubicin.

There were six children who did not complete the planned courses of vitamin E or placebo. Three did not complete the planned courses of study medication because of discontinuation of doxorubicin. One child with an intracranial lymphoma experienced severe mucositis after her first cycle of doxorubicin (placebo), and therefore doxorubicin was subsequently discontinued. She was the only patient to have a reduction in chemotherapy attributable to mucositis. Doxorubicin was discontinued prematurely in the second child after the third cycle because of cardiac dysfunction. One adolescent had progressive Ewing's sarcoma after the first cycle (placebo) and went on to die of progressive disease without receiving further doxorubicin. Three children chose to discontinue the study medication related to dislike of medication administration. Two received only a single cycle of study medication (active in one child and placebo in a second child), while one child discontinued study medication after two cycles (one active and one placebo).

In total there were 45 cycles of study medication administered: 4 children received 1 cycle, 5 children received 2 cycles, 1 child received 3 cycles, 4 children received 4 cycles and 2 children received 6 cycles. Active drug was administered in 22 cycles and placebo was administered in 23 cycles. Of these 45 cycles, filgrastim was used in 20/22 (91%) vitamin E cycles and in 21/23 (91%) placebo cycles. High dose methotrexate preceded study drug administration in five cycles of vitamin E (12 g/m^2; $n = 4$ and 8 g/m^2; $n = 1$) and in six cycles of placebo (12 g/m^2; $n = 5$ and 8 g/m^2; $n = 1$). The dose of doxorubicin was 75 mg/m^2 in 44 cycles and 60 mg/m^2 in one cycle (placebo). Administration of doxorubicin was continuous (in contrast to bolus) in 16/22 (73%) of active cycles and 18/23 (78%) of placebo cycles. Prophylactic acyclovir was administered to one child in each group. An oral swab for herpes simplex virus PCR was available at day 10 or 14 of each cycle and only one swab (placebo) was positive.

Table 1 illustrates the main results of this study. For the primary outcome, the objective mucositis score measured on days 7, 10 14 and 17, the observed average mucositis score associated with vitamin E was 0.1 units less (0.2 for vitamin E and 0.3 for placebo on a scale of 0–5) than the average mucositis score associated with placebo. Vitamin E was associated with a ratio of mean scores of 0.90 (95% CR 0.57, 1.37). There was a 73% probability that vitamin E was associated with less mucositis than placebo, which did not meet our *a priori* defined criteria of >95% probability for evidence of efficacy. In terms of our *a priori* defined evidence of a clinically important difference, there only was a 35% probability that vitamin E was associated with at least a 20% decrease in mucositis (i.e., that the ratio of means was less than 0.8). Fig. 1 demonstrates the posterior distribution of the ratio of mean scores, where portions of the curve to the left of 1 are values indicating that vitamin E was associated with less mucositis.

Table 2 illustrates the results of the sensitivity analysis to different prior distributions for the treatment effect for the primary outcome measure. No matter which prior distribution was used, the probability that vitamin E was effective by a clinically significant amount (ratio of means less than 0.8, meaning at least a 20% reduction) was not convincing. Since the uninformative prior leads to a low posterior probability of a clinically important effect, the sceptical prior gives an even lower probability (26%) of such an effect. The optimistic prior centred at a ratio of means of 0.8, which puts 50% prior probability on values less than 0.8, leads to a posterior probability of only 42% on values less than 0.8.

Table 1 – Mucositis outcomes by topical vitamin E versus placebo allocation

Characteristic	Descriptive		Model based		
	Vitamin E cycles (N = 22)	Placebo cycles (N = 23)	Posterior mean of R[a] (95% CR)	Prob (R < 1)[b]	Prob (R < 0.8)[b]
Objective mucositis score; mean score per cycle (95% CI)	0.2 (0.0, 0.3)	0.3 (0.0, 1.5)	0.90 (0.57, 1.37)	0.73	0.35
Pain visual analogue scale; mean score per cycle (95% CI)	0.9 (0.2, 2.1)	0.9 (0.0, 2.4)	1.08 (0.82, 1.36)	0.31	0.01
Swallowing visual analogue scale; mean score per cycle (95% CI)	1.3 (0.2, 2.5)	1.0 (0.0, 2.8)	1.38 (1.06, 1.77)	<0.01	<0.01
World Health Organization scale; mean score per cycle (95% CI)	0.4 (0.0, 1.1)	0.4 (0.0, 1.2)	1.19 (0.89, 1.57)	0.13	<0.01

Abbreviation: CI – confidence interval; CR credible region; R-ratio of the mean score in the vitamin E group to the mean score in the placebo group.

a Mean scores are descriptive and not model based. Posterior mean of R is model based and was calculated using a hierarchical Bayesian model – see Section 2.

b Values of the ratio of means (R) less than 1 represent a reduction in the mean score with vitamin E relative to placebo. Values of R less than 0.80 represent at least a 20% reduction in the mean score with vitamin E relative to placebo.

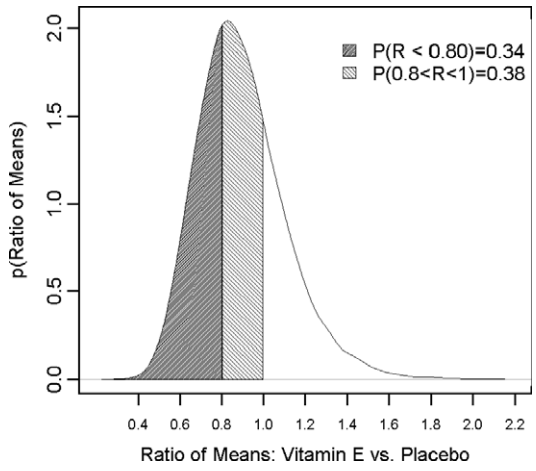

Fig. 1 – Posterior distribution of the ratio of means for the objective mucositis score. A ratio of mean scores of 1 suggesst that vitamin E and placebo are associated with the same amount of mucositis, while areas to the left of 1 suggest that vitamin E is associated with less mucositis. The shaded area to the left of R = 0.8 (a clinically important reduction) is 0.34 and represents the posterior probability of a reduction by a clinically important amount.

Table 1 also illustrates that vitamin E was not associated with a reduction in pain VAS scores, with mean scores of 0.9 (on a scale of 0–10) in each group with a ratio of mean scores of 1.08 (95% CR 0.82, 1.36). There was only a 31% probability that vitamin E reduced pain and a 1% chance that vitamin E was associated with a clinically significant decrease in pain VAS scores (i.e. a ratio of mean scores less than 0.8). Similarly, vitamin E did not reduce difficulty with swallowing, and the chance that vitamin E was better than placebo was <1%. Finally, the WHO mucositis scores were similar in the vitamin E and placebo cycles, with mean scores of 0.4 in each group. Of the 16 participants, 13/16 (81%) had any mucositis during one of the study cycles according to the WHO scale. Of the 657 subjective assessments performed, the proportion of days with any mucositis according to the WHO scale was 88/333 (26%) in the vitamin E group and 84/324 (26%) in the placebo group. The proportion of days with severe mucositis (WHO grade 3 or 4) was low and was similar in the vitamin E (5/324, 1.5%) and placebo (7/333, 2.1%) groups.

Table 3 illustrates the other secondary outcomes. The vitamin E and placebo cycles were associated with a similar proportion receiving opioid analgesia. Based on our model, there was only a 19.5% probability that vitamin E was associated with less opioid use than placebo. For the other outcomes, because of the small number of cycles in which these outcomes were experienced, these outcomes were not modelled. The two groups were associated with a similar number receiving topical oral analgesia, intravenous hydration, parenteral nutrition, and febrile neutropenia. There were two episodes of bacteremia while subjects received study medication. Both occurred during placebo cycles and occurred in different patients, with one patient having viridans group *Streptococcus* and another patient having *Escherichia coli*. Both patients survived the episode.

There were 630 planned doses of study medication, of which 98 were missed, resulting in a compliance of 84%. Non-compliance was twice as common in vitamin E cycles compared with placebo, with a non-compliance proportion of 64/308 (21%) for vitamin E and 34/322 (11%) for placebo.

Table 2 – Sensitivity analysis to different prior distributions for the treatment effect R for objective mucositis scores

Prior mean	Prior 95% CR[a]	Posterior mean (95% CR)	Posterior Prob (R < 1)[b]	Posterior Prob (R < 0.8)[b]
Sceptical				
Means are equal in vitamin E and placebo group	0.5–2.0	0.92 (0.62, 1.31)	0.70	0.26
Optimistic				
Vitamin E results in a 20% reduction in mucositis (ratio of means R = 0.8)	0.6–1.07	0.83 (0.64, 1.05)	0.95	0.42

a The prior 95% CR is a set of values containing 95% of our prior belief.
b Values of the ratio of means (R) less than 1 represent a reduction in the mean mucositis score with vitamin E relative to placebo. Values of R less than 0.80 represent at least a 20% reduction in the objective mucositis score with vitamin E relative to placebo.

Table 3 – Other secondary outcomes by treatment arm

Characteristic	Vitamin E Cycles (N = 22)	Placebo cycles (N = 23)
Number of cycles in which opioid analgesia was administered	11 (50%)	9 (39%)
Average opioid use per cycle expressed per kilogram (95% CI)	0.1 (0.0, 1.1)	0.4 (0.0, 4.7)
Number of cycles in which topical analgesia was administered	2 (9%)	2 (9%)
Number of cycles in which intravenous fluid was administered	4 (18%)	3 (13%)
Requirement for parenteral nutrition	0	2 (9%)
Febrile neutropenia	6 (27%)	8 (35%)
Bacteremia	0	2 (9%)

Overall, based on our model for compliance, there was an 82% probability that compliance was worse on vitamin E. In absolute terms, 12 of 16 subjects had worse compliance on vitamin E.

There was no unexpected toxicity associated with topical vitamin E administration. Many children complained that the study solution was difficult to use because of the oily texture.

There was added complexity to the *N*-of-1 design, since careful documentation of which study cycle each child was undergoing was imperative. Nonetheless, the study was completed without difficulty.

4. Discussion

There are two important findings from our study. First, our study demonstrates that topical vitamin E does not prevent mucositis by a clinically important amount in children receiving similar intensity of doxorubicin-containing chemotherapy. Second, our study demonstrates that it is feasible to use this alternate trial design (Bayesian *N*-of-1 design) to evaluate interesting interventions in a rigorous fashion (i.e. randomised allocation and blinded assessment) with a limited sample size without having to conduct a full scale trial. This second point may have important implications to the evaluation of many interventions in paediatric cancer in which an intervention is targeted at a relatively small sub-group or a relatively rare condition.

Our results are discordant with those of Lopez et al.[7] who did demonstrate a benefit to vitamin E. It is possible that we did not demonstrate a treatment benefit because the proportion of cycles with severe mucositis was low. Nonetheless, we believe that our trial represents the expected magnitude of mucositis in children undergoing doxorubicin-containing chemotherapy. Second, it is possible that the difference in our results was related to different ages in the two study populations. However, there is no biological reason to believe that vitamin E efficacy should be different in adults compared with children.

There were disadvantages of our methodological approach of *N*-of-1 trials combined with Bayesian analysis. These disadvantages include the general unfamiliarity with these methods and additional difficulties with the analysis – in part because 'off the shelf' techniques similar to *t*-tests and χ^2 are not available. Nonetheless, these disadvantages were out-weighed by the benefits, which include the ability to maximise information from each participant (since each participant could contribute information for almost all doxorubicin cycles in contrast to a typical parallel group design), the ability to directly compute the probability that vitamin E was effective, and the ability to estimate the probability that vitamin E was effective by a clinically important amount. The Bayesian approach also allowed us to address issues of interpretation. Even from the point of view of a person who is optimistic about the efficacy of topical vitamin E, the results of this trial indicate that there is a less than 50% chance that vitamin E is effective by a clinically important amount. The model in this paper may appear complex but only part of the complexity is due to the use of the Bayesian *N*-of-1 design. Generalised linear models using gamma-distributed outcomes have been used for many years in non-Bayesian statistics.[13]

We could have chosen alternative approaches to analysing the data, such as calculating the area under the curve (AUC) for mucositis scores over time. However, we chose not to use this approach as the AUC does not make use of all the data since it summarises each child's treatment course into a single value. In addition, AUCs are difficult to interpret clinically.

Some may be concerned about the sample size of our study and consequently its external validity or generalisability. However, our study is the largest randomised controlled trial of vitamin E prophylaxis to date, and when including the number of randomised study cycles, our trial is the largest published study of vitamin E in relation to mucositis. Furthermore, the participants in our study had a variety of underlying diagnoses, age and gender, and thus, we believe that our results are generalisable to children in our included age range who are receiving at least 60 mg/m^2 of doxorubicin.

In summary, topical vitamin E did not reduce mucositis in children receiving doxorubicin-containing chemotherapy and should not be used in the clinical context for this purpose. The use of an alternative trial methodology, namely *N*-of-1 trials and Bayesian analysis, can be successfully performed.

Conflict of interest statement

None of the authors have any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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Appendix 1. Details of model

The gamma distribution, like the normal distribution, has two parameters. There are several ways in which the gamma distribution can be indexed by these two parameters. A convenient way for our purposes is to have one parameter as the shape and the other as the mean. As suggested by its name, the shape parameter affects the shape and skewness of the curve. It is the ability of the gamma distribution to represent various shapes of distribution that make it particularly useful for analysis of skewed data.

Following McCullagh and Nelder[14], we modelled the outcomes such that there was a common shape parameter for all observations and a mean parameter that depended on

the characteristics of the particular observation. With patients identified by ID and time period by t (so that the outcomes are represented as $Y_{ID,\ t}$), our model was

$$Y_{ID,t} \sim \text{Gamma}(\text{shape}, \text{mean}_{ID,t})$$

As usual we built a regression model for the mean.

$$\log(\text{mean}_{ID,t}) = \alpha_{ID} + \beta * \text{TMT}_{ID,t} \quad (1)$$

or equivalently

$$\text{mean}_{ID,t} = \theta_{ID} * \exp(\beta \text{TMT}_{ID,t}), \quad \text{where } \theta_{ID} = \exp(\alpha_{ID})$$

Here, $\text{TMT}_{ID,t}$ is equal to 1 when patient ID received vitamin E on occasion t and $\text{TMT}_{ID,t} = 0$ when the patient received placebo. Because the natural logarithm of the mean is expressed as a regression equation, the effect of treatment on the mean response is multiplicative. The mean response for subject ID on placebo is θ_{ID} and the mean on vitamin E is $\theta_{ID} * \exp(\beta)$. Repeat observations on subject ID will be 'clustered' around these means.

The parameters α_{ID} are the log-means for subjects while on placebo. We assume that these values are centred on an overall (population) mean α_0 with a standard deviation σ_α:

$$\alpha_{ID} \sim N(\alpha_0, \sigma_\alpha) \quad (2)$$

Both of these unknowns are estimated from the data.

The above development shows the overall structure of our random effects model with gamma distributed outcomes. The specific details of the predictors in the regression model (1) were different for the different outcomes. For the objective measure in which assessments occurred four times per cycle, it was known *a priori* that mucositis waxed and waned over the course of treatment, so day of assessment (with values of 7, 10, 14 and 17) was included as a categorical variable. For subjective scores, since there were 16 observations per cycle, we adjusted for the anticipated increase and then decrease in scores over the 16 days by adding to (1) linear and quadratic terms for day:

$$\log(\text{mean}_{ID,t}) = \alpha_{ID} + \beta * \text{TMT}_{ID,t} + \gamma_1 * \text{day}_{ID,t} + \gamma_2 * \text{day}^2_{ID,t}$$

where $\text{day}_{ID,t}$ is the tth day of observation for subject ID.

In these models, the effect of vitamin E at any particular time for any particular subject is the constant ratio of means:

$$R = \frac{\text{mean on treatment}}{\text{mean on placebo}} = \frac{\theta_{ID} * \exp(\beta + \text{predictors})}{\theta_{ID} * \exp(\beta * 0 + \text{predictors})} = \exp(\beta)$$

Therefore, the ratio of the mean in the treated group to the mean in the placebo group is $R = \exp(\beta)$. If high scores denote more mucositis, R less than one suggests that vitamin E is associated with less mucositis.

For each Bayesian analysis, we used non-informative priors. Specifically, we used diffuse priors for the shape

$$\text{shape} \sim \text{Exponential}(\text{rate} = 1)$$

the common intercept

$$\alpha_0 \sim N(\text{mean} = 0, \text{variance} = 10^6).$$

and σ_α the standard deviation of the random intercept. The prior distribution for the coefficient for treatment effect (β) was also assumed to be normal with a mean value of 0; however, we chose a variance of beta such that there was a 95% prior probability that $R = \exp(\beta)$ was between 0.1 and 10. We also performed a sensitivity analysis with different priors for R. We repeated the analysis using (a) a sceptical prior, centred at $R = 1$ and putting 95% prior probability on R being between 0.5 and 2 and (b) an optimistic prior centred at $R = 0.8$ and putting 95% prior probability on R being between 0.6 and 1.07.

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