

Reanalysis of morphine consumption from two randomized controlled trials of gabapentin using longitudinal statistical methods

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Background: Postoperative pain management in total joint replacement surgery remains ineffective in up to 50% of patients and has an overwhelming impact in terms of patient well-being and health care burden. We present here an empirical analysis of two randomized controlled trials assessing whether addition of gabapentin to a multimodal perioperative analgesia regimen can reduce morphine consumption or improve analgesia for patients following total joint arthroplasty (the MOBILE trials).

Methods: Morphine consumption, measured for four time periods in patients undergoing total hip or total knee arthroplasty, was analyzed using a linear mixed-effects model to provide a longitudinal estimate of the treatment effect. Repeated-measures analysis of variance and generalized estimating equations were used in a sensitivity analysis to compare the robustness of the methods.

Results: There was no statistically significant difference in morphine consumption between the treatment group and a control group (mean effect size estimate 1.0, 95% confidence interval -4.7, 6.7, $P=0.73$). The results remained robust across different longitudinal methods.

Conclusion: The results of the current reanalysis of morphine consumption align with those of the MOBILE trials. Gabapentin did not significantly reduce morphine consumption in patients undergoing major replacement surgeries. The results remain consistent across longitudinal methods. More work in the area of postoperative pain is required to provide adequate management for this patient population.

Keywords: postoperative morphine consumption, randomized controlled trials, gabapentin, reanalysis

Introduction

Major surgery, such as total hip arthroplasty (THA) and total knee arthroplasty (TKA), leads to acute and chronic postoperative pain in 10%–50% of patients.¹ Unrelieved pain after surgery increases heart rate, systemic vascular resistance, and circulating catecholamines, placing patients at risk of myocardial ischemia, stroke, bleeding, and other complications.¹ A number of strategies have been used to provide adequate analgesic effects in this target population, including wound infiltration with local anesthetic, peripheral nerve blockade with local anesthetic, epidural local anesthetic, oral or injectable nonsteroidal anti-inflammatory drugs, and systemic opioids (intravenous, intermittent, or patient-controlled analgesia).^{2,3} Although each of the abovementioned strategies has advantages and shortcomings, there has been a shift in anesthesiology towards the use of a combination of these strategies, often termed multimodal analgesia. Multimodal analgesia is defined as the use of a combination of opioids and nonopioids

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to manage postoperative pain, with the rationale behind such intervention being to achieve sufficient analgesia due to additive effects, while minimizing the doses of the individual drugs.^{2,4} This also has the advantages of a more rapid recovery, shortened hospitalization time, and improved patient functioning. Multimodal analgesia will not only allow for better patient pain management while reducing side effects, but can also significantly reduce health care costs.

The MOBILE (Morphine consumption in joint replacement patients, with and without gabapentin treatment, a randomized controlled study) trials⁵ were designed to assess whether the addition of gabapentin, an anticonvulsive drug traditionally used for chronic pain management, to a multimodal perioperative analgesia regimen can reduce postoperative morphine consumption or improve analgesia following THA or TKA. Secondary outcomes such as pain score, range of motion, and side effects were also compared. Previous randomized controlled trials and a meta-analysis⁶ of eight placebo-controlled randomized trials showed that gabapentin reduced pain scores, opioid consumption, and other side effects. However, in the MOBILE trials, the primary outcome of 72-hour cumulative morphine consumption was not significantly different between the gabapentin and control groups.⁵ There are a number of differences in these studies, including the patient population (different types of surgery) and the strategy involved in the use of gabapentin (multimodal analgesia versus other). Another potential source of variability in trial results is the method of analysis used. The method used for the statistical analysis can have a substantial influence on the statistical power and sample size of the trial.^{7,8}

The primary objective of this study was to conduct an empirical reanalysis of the MOBILE trials by analyzing the primary outcome, ie, morphine consumption, in a longitudinal manner rather than to treat the outcome as one cumulative score.⁸⁻¹⁰ More specifically, if the primary outcome of 72-hour cumulative morphine consumption was analyzed longitudinally, instead of cross-sectionally, would the result of no treatment difference remain robust? Morphine consumption, which was measured for four time periods, is analyzed here using a linear mixed-effects model (LMEM with a first-order autoregressive covariance matrix structure [AR(1)]. Secondary outcomes of this study include a number of sensitivity analyses to determine the robustness of the results based on longitudinal method of choice, method of handling missing data, and choice of covariance matrix structure. Specifically, to determine the sensitivity to method of analysis, sensitivity analyses with two other longitudinal methods,

ie, repeated-measures analysis of variance and generalized estimating equations (GEEs),¹⁰ assuming AR(1) covariance structure, are tested. The robustness of the method of handling missing data is determined by conducting a sensitivity analysis using a complete-case analysis. Lastly, two sensitivity analyses are conducted to determine the robustness of the covariance matrix structure when using LMEM, ie, compound symmetry and unstructured covariance structures.

Materials and methods

This is a statistical reanalysis of the data from the MOBILE trials⁵ to determine whether the statistical method had a major impact on the results.

Description of MOBILE trial

Total knee arthroplasty

In a single-center, blinded, placebo-controlled study, 102 patients were randomized to receive either gabapentin or placebo, in addition to standard of care, 2 hours before undergoing TKA.⁵ Morphine consumption, a continuous outcome, was recorded at four specific time points. The four time periods were: at the post-anesthesia care unit (time 0), 24 hours after surgery (time 1), 48 hours after surgery (time 2), and 72 hours after surgery (time 3). The statistical analysis was done by combining the morphine consumption for these four time periods and using a Student's *t*-test to compare the treatment group difference in cumulative 72-hour morphine consumption.

Total hip arthroplasty

In a single-center, blinded, placebo-controlled study, 101 patients were randomized to receive either gabapentin or placebo, in addition to standard of care, 2 hours before undergoing THA. Morphine consumption, a continuous outcome, was recorded at four specific time points. The four time periods were: at the post-anesthesia care unit (time 0), 24 hours after surgery (time 1), 48 hours after surgery (time 2), and 72 hours after surgery (time 3). The statistical analysis was done by combining morphine consumption for these four time periods and using a Student's *t*-test to compare the treatment group difference in cumulative 72-hour morphine consumption.

Data analysis

Data from the MOBILE trials⁵ were obtained to conduct the analysis of the primary outcome of morphine consumption in its longitudinal form. The data for the two trials were kept separate and the morphine consumption of patients who underwent TKA or THA was analyzed separately.

A total of 203 (101 and 102 patients for knee and hip replacement, respectively) patients were included in this reanalysis and missing data were imputed using multiple imputation to enable intention-to-treat, where all patients randomized in the study were included in the analysis.

The multiple imputation (MI) process included a number of variables from the trial and all these variables, including the morphine consumption outcome, were imputed in a similar manner, using the Markov chain Monte Carlo method.^{11,12} Five iterations of the MI process were included and a combined treatment estimate was generated at the end. The baseline variables included for the MI process were: sex, weight, height, American Society of Anesthesiologists score, systolic blood pressure, diastolic blood pressure, pain at rest during the four time periods, pain with passive movement at the time points, and pain on weight-bearing at the time points. These variables were included in the MI strategy to have the most complete imputation method without any bias.

The treatment estimate between the control group and the experimental group was determined using LMEM, with a covariance structure of first-order autoregressive. All statistical tests were performed using SAS version 9.2 software (32-bit version, SAS Institute Inc., Cary, NC, USA).

Sensitivity analyses

Three robustness tests were conducted for the secondary objective of the study, one for the two other longitudinal methods, one for handling of missing data, and the last one for the use of different covariance matrix structures when analyzing by LMEM.

Robustness of repeated-measures analysis of variance and GEE

Two additional longitudinal methods were used to test the robustness of the results obtained from LMEM, namely repeated-measures analysis of variance (RM-ANOVA)⁹ and GEE.¹⁰ The sensitivity analysis was done by first analyzing the results using these two additional methods and qualitatively comparing the results in terms of direction of effect (sign), magnitude of effect (number), and precision of effect (*P*-value). The robustness of the method was then determined based on the above three criteria.

Robustness of complete-case analysis

To compare whether the results were affected qualitatively by implementation of MI, the results obtained by complete-case analysis for each of the longitudinal methods were used as the

comparator.^{11,12} The robustness test was done by comparing the two types of data handling methods based on a number of factors, including direction and magnitude of effect and precision of estimate. To further illustrate the difference between the two missing data handling methods, a forest plot of the 95% confidence interval (CI) of each of the six analyses was used to provide a visual comparison.

Robustness of compound symmetry and unstructured covariance matrices in LMEM

The results of LMEM using AR(1) were qualitatively compared with compound symmetry and unstructured covariance.¹³ For the purposes of this robustness test, both patient groups were used but only the MI results were included. The robustness test was done by comparing the different covariance matrix structures based on a number of factors, including direction and magnitude of effect and precision of estimate. To further illustrate the difference between the LMEM and the two analysis methods, a forest plot of the 95% CI for each of the six analyses was used to provide a visual comparison.

Results

In the TKA trial, there were 52 patients in the gabapentin group and 49 patients in the placebo group.⁵ The mean patient age was 62.1 years in the gabapentin group, with 63.4% of the patients being female. In the placebo group, the mean patient age was 63.5 years and 63.3% were female. Further baseline characteristics can be found in the MOBILE TKA trial.⁵

In the THA trial, there were 48 patients in the gabapentin group and 54 patients in the placebo group. The mean patient age was 61.4 years in the gabapentin group, with 41.7% of the patients being female. In the placebo group, the mean patient age was 60.9 years and 44.44% were female. Additional baseline characteristics can be found in the MOBILE THA trial.

Analysis of morphine consumption for four time periods

In patients undergoing TKA (*n*=101), the mean effect size estimate obtained was 1.0 (95% CI -4.7, 6.7; *P*=0.73) between the groups when the analysis was performed with LMEM and MI. There was no statistically significant difference in morphine consumption between the gabapentin and control group.

In patients undergoing THA (*n*=102), the mean effect size estimate obtained was -1.0 (95% CI -5.4, 3.3; *P*=0.63) between the groups when the analysis was performed

with LMEM and MI. There was no statistically significant difference in morphine consumption between the gabapentin and control groups (see Table 1).

Sensitivity analyses

Sensitivity to method of analysis

The primary method used for analysis of the longitudinal morphine consumption data was LMEM, with MI as the method for handling missing data. Compared with the results for the TKA and THA patients generated from LMEM, the results obtained by RM-ANOVA and GEE remained robust and the overall findings were consistent across methods (Figures 1 and 2). More specifically, the direction, magnitude, and precision were similar across all three methods. The two comparator methods had a slightly tighter 95% CI and *P*-value.

Sensitivity to missing data

There was a slight discrepancy in results between the TKA and THA patients, and their results are reported separately.

In patients undergoing TKA (*n*=101), there were 38 datum points (9%) missing across the four time periods for the TKA patients, with only two patients missing all datum points. The missing data did not show a monotone pattern, where subsequent morphine consumption values were not necessarily missing for subsequent time periods. For the TKA patients, with LMEM, the complete-case analysis had a mean effect estimate of -0.85 (95% CI $-7.1, 5.4$; *P*=0.84). Comparing with the LMEM analysis using MI, the direction of the effect estimate from the complete-case analysis was opposite; however, with such wide 95% CIs and the near zero effect estimates, the direction of effect cannot be said to have changed. The magnitude was similar, both being very close to 0. The complete-case analysis had a wider 95% CI and a larger *P*-value than the MI analysis.

In patients undergoing THA (*n*=102), there were 30 datum points (7%) missing across the four time periods for the THA patients. The missing data did not show a monotone pattern,

where subsequent morphine consumption values were not necessarily missing at subsequent time points. For the THA patients, complete-case analysis with LMEM generated similar results as those with MI. The direction, magnitude, and precision of the estimates were all similar to the MI analyses, and none of the comparisons revealed statistically significant differences.

Sensitivity to covariance matrix

Changing the covariance matrices in the LMEM analysis had no qualitative effect on the results generated. The results of the LMEM analysis remained robust and findings were consistent regardless of the covariance matrix used. Qualitatively, using the unstructured covariance matrix provided the highest precision via a tighter 95% CI and lower *P*-value, which was the case for both patient groups.

Discussion

Key clinical finding

In the present study, morphine consumption in the gabapentin and control groups from the MOBILE trials was compared and the results suggested that there was no statistically significant difference in morphine consumption following TKA or THA. Unlike the original analysis of the MOBILE trials,⁵ the present study analyzed the primary outcome of morphine consumption longitudinally, where an additional time factor was incorporated into the statistical model. Nonetheless, the results are consistent with the results of the MOBILE trials,⁵ where no statistically significant difference in morphine consumption was found between the placebo and gabapentin groups. For instance, in the knee study, the difference in 72-hour cumulative morphine consumption was -6.18 mg (95% CI $-29.11, 16.76$; *P*=0.593).⁵ From the longitudinal reanalysis of this study, the difference in morphine consumption for the four time periods was 1.0 mg (95% CI $-4.7, 6.7$; *P*=0.73).

However, it should be noted that there have been a number of other studies suggesting the efficacy of gabapentin as analgesia in postoperative pain management.^{6,14,15} Meta-analysis and studies at the molecular level indicate that gabapentin can help to reduce morphine consumption and attenuate the side effects of opioids. Therefore, further trials are needed to evaluate gabapentin and build up a body of evidence regarding the use, dosage, and timing of gabapentin administration in the management of postoperative pain.

Key methodological findings

The current study addresses a number of methodological issues related to longitudinal studies. Analysis of longitudinal data,

Table 1 Results of longitudinal analysis of morphine consumption in two studies using LMEM

Trial/patients	Effect estimate	95% CI	<i>P</i> -value
TKA (<i>n</i> =102)	1.0	-4.7, 6.7	0.73
THA (<i>n</i> =101)	-1.0	-5.4, 3.3	0.63

Notes: Differences in treatment effect between the placebo and intervention groups was not statistically significant for either TKA or THA patients. TKA and THA analyses done with multiple imputation (*m*=5).

Abbreviations: CI, confidence interval; LMEM, linear mixed effects model; MI, multiple imputation; THA, total hip arthroplasty; TKA, total knee arthroplasty.

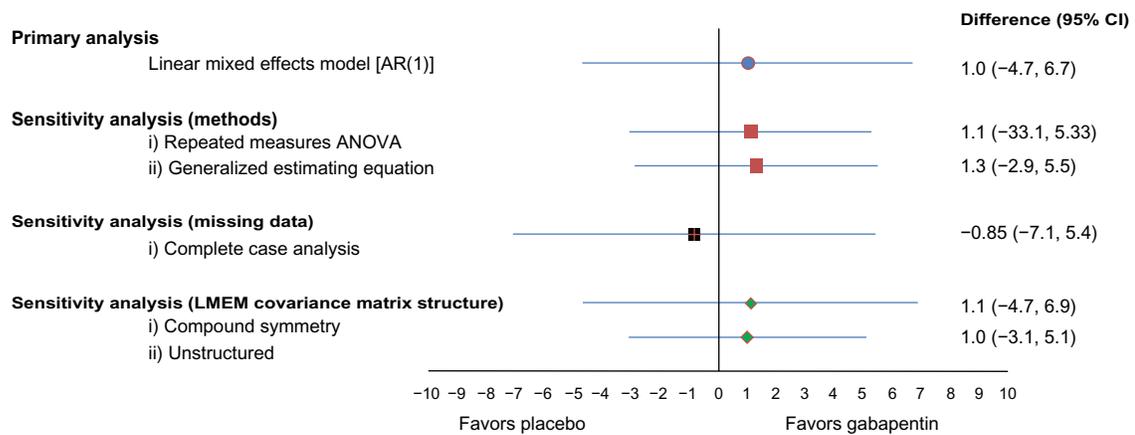


Figure 1 Results from three sensitivity analyses conducted for the secondary objective of this study in patients undergoing TKA.

Notes: Specifically, the three analyses were of the robustness of the longitudinal method (repeated-measures ANOVA and GEE), the robustness of the method of handling missing data (complete-case analysis), and the robustness of the covariance matrix structure in LMEM. The difference between postoperative morphine consumption was not statistically significant in patients undergoing TKA. Further, the results were robust across statistical methods, methods of handling missing data, and LMEM covariance matrix structures. More specifically, the magnitude, direction, and precision of effect were qualitatively similar.

Abbreviations: AR(1), autoregressive covariance matrix structure; ANOVA, analysis of variance; CI, confidence interval; GEE, generalized estimating equations; LMEM, linear mixed effects model; TKA, total knee arthroplasty.

which are repeated measures of the same subject over a period of time, has always been an important part of clinical research. Subject-specific and population-average methods exist for the analysis of longitudinal data, and in the present study, three methods, ie, two subject-specific methods and one population-average method, were used to analyze morphine consumption. Using the three methods, morphine consumption was not significantly different between the two treatment arms across the two patient populations. Moreover, the results generated from RM-ANOVA and GEE had the same direction and magnitude of effect when compared with LMEM. The precision of the results also remained similar across methods.

The robustness of any statistical test can be used as a measure of how the results differ by varying statistical assumptions, parameter, and other study factors. For instance, the robustness to missing data can be measured by changing the method of handling missing data (such as complete-case analysis, multiple imputation, and single imputation). If the results remain the same, it can be said that the results are robust and the conclusion drawn is strengthened.

Appropriate handling of missing data is important because these can potentially affect the conclusion drawn. Analysis of longitudinal data with a classical linear model restricts the analysis to participants with complete data

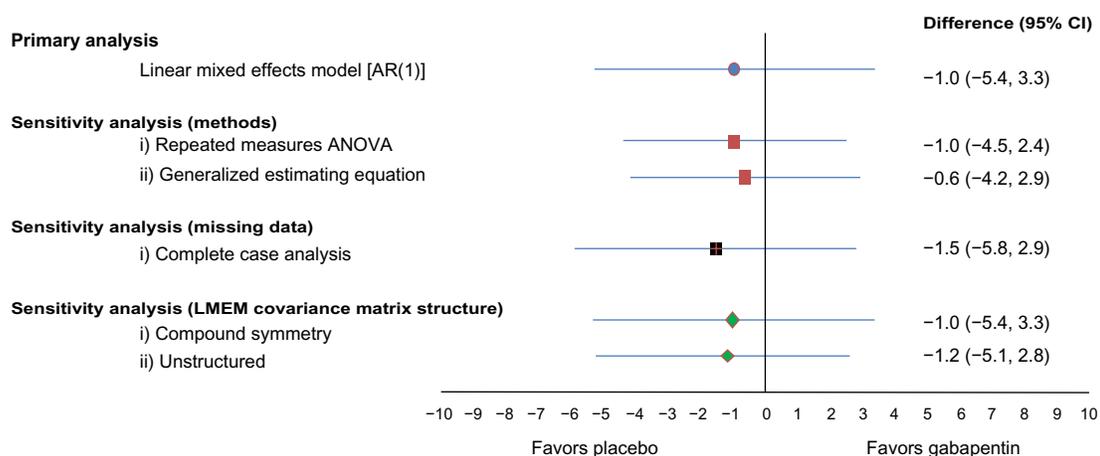


Figure 2 Results from the three sensitivity analyses conducted for the secondary objective of the study for patients undergoing THA.

Notes: Specifically, the three analyses were of the robustness of the longitudinal method (repeated-measures ANOVA and generalized estimating equations), the robustness of the method for handling missing data (complete-case analysis), and the robustness of the covariance matrix structure in LMEM. The difference between postoperative morphine consumption was not statistically significant in patients undergoing THA. Further, the results were robust across statistical methods, methods of handling missing data, and LMEM covariance matrix structures. More specifically, the magnitude, direction, and precision of effect were qualitatively similar.

Abbreviations: AR(1), autoregressive covariance matrix structure; ANOVA, analysis of variance; CI, confidence interval; LMEM, linear mixed effects model; THA, total hip arthroplasty.

for all time points. When the missing data are not missing completely at random, the results of complete-case analysis may be biased because the complete case may be unrepresentative of the total population. An effective method of dealing with missing data is to conduct MI. All of these methods require the data to be missing at random. In our study, the results for each method of handling missing data (MI or complete-case analysis) yielded similar conclusions, ie, that there was no difference between the two treatment groups. Moreover, this conclusion regarding the robustness of the different methods of handling missing data was consistent between the two patient populations who underwent TKA and THA. Numerous studies have compared parametric models using likelihood functions and semiparametric models using GEE, both with and without MI, in the context of incomplete longitudinal data.^{11,12} The results of the present study were consistent with previous research, although not perfectly comparable since a qualitative approach was employed in our study.

Our primary analysis used LMEM with AR(1), because of our hypothesis that morphine consumption would likely decrease on a daily basis and readings separated by a longer temporal period are less correlated with each other. Although AR(1) implies that observations for the same patient far apart in time would be essentially independent and this may not be truly realistic, with only four repeated measures in this study, we still thought AR(1) represented the most appropriate covariance structure for the model. The results remained robust across changes in covariance structure in LMEM. Although the literature suggests use of AR(1) since this covariance model provides a good fit compared with unstructured covariance structure,¹³ the present study did not show any quantifiable difference. Nevertheless, our results agree with previous studies, where the estimate of fixed effect, in this case a difference between the two treatment groups, remains the same for different covariance structures.

One of the key limitations of this study is the assumption of missing at random. The mechanism of missingness plays an important role in determining the most appropriate statistical method and imputation method. GEE treats covariance structure as a nuisance and variance of data is not of concern when analyzing data under GEE.^{9,11} However, GEE often performs poorly unless the mechanism of missing data is missing completely at random. Similarly, MI assumes that the mechanism of missingness is missing at random. However, no test was conducted in this study to determine the mechanism of missing data and these assumptions may not hold true. Testing for the mechanism of missing data is often difficult,

especially with a lack of auxiliary information, such as the demographic and social characteristics of the participants. Missingness was assumed to be missing at random in this study because of the low percentage of missing data (7% and 9% in THA and TKA patients, respectively) and the lack of a monotone pattern in the missing data. Moreover, the robustness of the complete-case analysis suggests that there was not a substantial amount of missing data.

Conclusion

This study compares three statistical methods for analyzing longitudinal data by applying the methods to an empirical dataset. Using morphine consumption taken for four different time periods, we were able to strengthen the conclusion from the MOBILE trials that there was no statistically significant difference in postoperative morphine consumption between the two treatment groups. Our study suggests that LMEM is not superior to GEE or RM-ANOVA in terms of statistical power on a qualitative level. Moreover, our results remained robust even when complete-case analysis was done, and mis-specification of the covariance structure did not affect the results.

Author contributions

LT, JP, MNA, and SZ conceived the idea and designed the study; SZ, LT, JP, MNA, NB, US, JC, JD, MW, DW, DP, and VA contributed to analysis and interpretation of data. SZ, LT, JP, MNA, NB, US, JC, JD, MW, DW, DP, and VA contributed to the acquisition of data. SZ, LT drafted the article. SZ, JP, MNA, NB, US, JC, JD, MW, DW, DP, VA, LT contributed to writing and critically revising the manuscript. All authors read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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