A longitudinal analysis of anesthesia data for cataract surgery: selection of working correlation structure

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Abstract

Background: Cataract surgery is most commonly done under local anesthesia with anesthesia and sedation controlled. Anesthetic depth and awareness monitoring during surgery frequently lead to irregular-timed observations. Inappropriate choice of working correlation structure in generalized estimating equations (GEE) may lead to inefficient estimation of parameters. The aim of this study was to apply the two new criteria to the anesthesia data for cataract surgery, to select and compare different candidates for working structure.

Methods: In this randomized controlled trial, anesthesia depth and hemodynamic changes were considered to be the primary outcome. The first group received propofol at a dose of 50-75 μg/kg/min and the second group received 1% isoflurane. We developed a GEE regression model based on several candidates for the working correlation framework and then evaluated it according to CEBIC (Constraint Empirical Bayesian Information Criterion) and CEAIC (Constraint Empirical Akaike Information Criterion) criteria. Data analysis was performed using the R software 3.6.1.

Results: The mean age of the propofol group was 67.46 years (SD = 12.46 years) and 64.53 years for the isoflurane group (SD = 13.77 years). The mean BIS in isoflurane was higher among all time points than the propofol group, but only the difference between the two groups was statistically significant in 3 min after surgery (P = 0.04). On the basis of the CEAIC and CEBIC criteria, an independent working correlation was the best structure for the BIS outcome. In addition, the best structure was the unstructured correlation for HR. The MAP (mean arterial pressure) parameter estimate results revealed that the AR (1) structure was a good choice.

Conclusion: In comparison to CIC and QIC, two CEAIC and CEBIC criteria have chosen a different structure for the working correlation between repeated measurements of anesthetic indices obtained during cataract surgery.

Keywords: Working correlation structure, Longitudinal data, Propofol, Isoflurane, Cataract, Anesthesia

Introduction

A cataract is the lack of clarity of the lens due to the opacification of the lens (Liu et al. 2017). In 2014, the WHO reported 95 million people were visually impaired due to cataracts (WHO 2014). Several large-scale population-based studies have reported that cataract prevalence increases with age, ranging from 3.9% at age 55–64 to 29.6% at age 80 and older (Mitchell et al. 1997; Chua et al. 2015; Varma and Torres 2004). The current visually significant cataract management standard is the surgical removal and replacement of the cataract lens with the intraocular lens. Cataract surgery is one of the most cost-effective treatments in many countries, and the most widely performed technique (Jaycock et al. 2009). Among low-income and middle-income countries, there is gender inequality in cataract surgical exposure, where men are more likely to have cataract...
surgery than women (Peto odds ratio [OR] 1·71, 95% CI 1·48–1·97) (Lewallen et al. 2009).

Cataract surgery is most frequently performed under local anesthesia with monitored anesthesia care and sedation (Alhashemi 2006; Eichel and Goldberg 2005). During this procedure, different medications were used for sedation, including propofol, benzodiazepines, and opioids (Aydin et al. 2002; Janzen et al. 1999; Wong and Merrick 1996). Propofol is a short-acting sedative with a quick recovery profile and its use is related with a number of additional benefits including the relative ease in retaining a sufficiently depressed level of consciousness and sufficient amnesia (Gotoda et al. 2016). Oxygen desaturation and hypotension, however, are limitations of propofol sedation. Care is needed to avoid sedation-related adverse events in the treatment of older patients because elderly people commonly have 1 or more underlying diseases (Alhashemi 2006; Gotoda et al. 2016). On the other hand, the bispectral index system (BIS, Aspect Medical Systems) has been developed and is currently broadly used to monitor the anesthetic depth and awareness or adequacy of anesthesia throughout the surgery (Wang et al. 2013). The worldwide market leader is the bispectral index system (BIS, Aspect Medical Systems), which notifies anesthesiologists if the anesthesia depth is insufficient (Orser 2008; Chen and Rex 2004). BIS monitoring is a system based on electroencephalography that measures the depth of anesthesia by measuring the electroencephalogram and utilizes a complex algorithm to produce an index score that offers an objective measurement of the level of consciousness in sedated patients (Drake et al. 2006; Imagawa et al. 2008; Johansen and Sebel 2000). Comparison of hemodynamic changes between both the propofol groups and isoflurane was inconsistent in most studies. Furthermore, the depth of anesthesia pattern across surgery has not been contrasted between classes.

Longitudinal observations often occur in the context of anesthesiology through anesthesia depth monitoring or hemodynamics. The well-known generalized estimating equation (GEE) offered by Liang and Zeger was a quite popular approach to the analysis of longitudinal data (Liang and Zeger 1986). GEE estimators are efficient when the structure of the working correlation is correctly defined. Nonetheless, failure to define this structure may lead to a significant loss of efficiency even though the quality can remain so (Wang and Carey 2003). In addition, anesthetic depth and awareness monitoring during surgery frequently produce in irregular timed observations. Wang et al. extended the GEE framework with two new criteria for selecting the best working correlation framework for irregularly timed measurements and small sample size results. The aim of this study was, therefore, to apply the two criteria introduced by Wang et al. to the data presented in (Khakzad et al. 2019), to select and compare different candidates for working correlation structure applying to cataract surgery data.

Methods
The GEE method was applied to data submitted by Khakzad et al. and collected using a randomized design of the clinical trial (Khakzad et al. 2019). We used the program code in version 3.6.1 of the R software program to analyze the data. The codes can be found in the Additional file 1. We built a GEE regression model based on several candidates for the working correlation structure. These candidate models were then compared according to CEBIC (Constraint Empirical Bayesian Information Criterion) and CEAIIC (Constraint Empirical Akaike Information Criterion) criteria and selected the best. In particular, since the values of the response variable is continuous in this study, we consider a Gaussian regression model where the mean structure is specified as

\[ \mu_{ij} = \beta_0 + \beta_1 \text{intervention} + \beta_2 \text{time} + \beta_3 \text{intervention} \times \text{time} \]

where, \( \mu_{ij} \) is the response mean for \( ith \) participant in time \( j, \beta_0, \beta_1, \beta_2, \text{and} \beta_3 \) are regression coefficients.

The RCT was approved by the Ethics Committee of the University Of Medical Sciences Of Babol. The Code of Ethics was MUBABOL.REC.1394.289. The RCT was registered on the irct.ir website and the code is IRCT20100208003305N9. Participants included 60 patients undergoing cataract surgery in class I and class II of the American Society of Anesthesiologists (ASA). Patients were ineligible to take part in this study if they had (a) a history of cardiovascular disease, (b) had diabetes and uncontrolled hypertension, (c) had liver or kidney failure, (d) patients with psychiatric problems, addicted to alcohol and drugs, and (e) patients with a difficult airway. Eligible patients were randomly divided into two intervention groups. One party administered 50-75 (μg/kg/min) of propofol and the other administered 1% of isoflurane (Soha Helal Company) to sustain anesthesia. Heart rate, systolic and diastolic blood pressure, and BIS were tracked and registered prior to induction. The BIS level (vista device) was recorded at baseline (before surgery), followed by 1, 3, 5, and 8 min after surgery, and then every 5 min, depending on the time of operation. At the end of the surgery, hemodynamics and BIS indices were also registered when anesthetics were stopped and laryngeal mask airways removed. In addition, wake-up time was reported from the time the medication was discontinued until the eyes were opened by a call, and recovery time was calculated from the time the medication was discontinued until the patient earned Aldrete scores higher than 9.
Further data on the RCT can be found in the article by (Khakzad et al. 2019).

Results
The mean age for the propofol group was 67.46 years (standard deviation (SD) = 12.46 years) and 64.53 years for the isoflurane group (SD = 13.77 years). The clinical trial included 16 (53.3%) males in the propofol group and 15 (50%) males in the isoflurane group. Of the participants, 5 (16.70%) were educated in the propofol group and 4 (13.30%) in the isoflurane group. General characteristics of the sample are shown in Table 1.

Average of BIS, HR, and MAP between the two intervention groups before and during cataract surgery was shown in Table 2. The mean BIS in isoflurane was higher among all time points than the propofol group, but only the difference between the two groups was statistically significant in 3 min after surgery ($P = 0.04$). On the other hand, the mean HR measurements in the propofol group were higher than isoflurane at all times, except for 23 min after surgery. The HR difference was only significant between the two intervention groups at the time 18 min after the start of the operation ($P = 0.02$). Although the MAP average was up to 5 min higher in the isoflurane group than in the propofol group, it was reversed 8 min later. At all times, the mean differences were not significant.

Tables 3, 4, and 5 provide an estimate of the regression parameters obtained using the GEE approach and standard errors in the four commonly working correlation structures (independence, exchangeable, AR (1), and unstructured). CEAIC, CEBIC, Correlation Information Criterion (CIC), and Quasi-likelihood Information Criterion (QIC) criteria were used to select the appropriate working correlation structure for each of the three outcomes. According to Table 3, for the BIS result, on the basis of the two new criteria, CEAIC and CEBIC, a lower value was obtained for the independent working correlation. Whereas according to the CIC criterion, the structure of AR (1) was best suited to the correlation of repeated measures. Under the independence structure, the standard errors of the estimates were smaller than those of the other correlations. Table 4 provided the calculation of regression coefficients for HR under specific working correlation structures. The results indicated that the unstructured correlation was the best structure based on the CEAIC and CEBIC criteria, while the AR (1) structure was selected by CIC and the independence correlation was selected by QIC. The parameter estimate results for MAP revealed that the AR (1) structure was a good choice based on CEAIC, CEBIC, and CIC, while the QIC criteria selected the exchangeable correlation structure (Table 5).

Discussion
In the present study, two new criteria were applied to select the true working correlation structure for irregular timed measurements. Measurements were collected from two groups of patients undergoing cataract surgery; randomized controlled trial participants were assigned to either propofol or isoflurane. Our results showed that

Table 1 General characteristics of study participants
(percentage or mean ± SD)

| Variables         | Propofol (n = 30) | Isoflurane (n = 30) |
|-------------------|-------------------|---------------------|
| Age (years)       | 67.46 ± 12.46     | 64.53 ± 13.77       |
| Weight (kg)       | 67.4 ± 14.33      | 68.63 ± 13.75       |
| Male gender (%)   | 16 (53.3)         | 15 (50)             |
| Educated (%)      | 5 (16.7)          | 4 (13.3)            |
| Comorbid disease (%) | 18 (60)   | 20 (66.7)           |

Table 2 Average trend of BIS, heart rate, and MAP during cataract surgery between two intervention groups

| Variables | Propofol (n = 30) | Isoflurane (n = 30) | P value |
|-----------|-------------------|---------------------|---------|
| Pre BIS   | 94.36 ± 2.95      | 94.40 ± 2.89        | 0.970   |
| BIS 1 min | 54.00 ± 12.56     | 56.46 ± 11.16       | 0.424   |
| BIS 3 min | 43.63 ± 9.70      | 49.40 ± 11.92       | 0.048   |
| BIS 5 min | 46.06 ± 10.95     | 47.53 ± 9.42        | 0.615   |
| BIS 8 min | 46.23 ± 9.29      | 48.26 ± 9.00        | 0.433   |
| BIS 13 min| 47.76 ± 9.40      | 48.00 ± 6.95        | 0.906   |
| BIS 18 min| 46.56 ± 8.35      | 47.3 ± 7.28         | 0.739   |
| BIS 23 min| 48.38 ± 13.58     | 48.80 ± 7.86        | 0.563   |
| BIS in LMA time | 84.86 ± 5.76 | 86.77 ± 4.23       | 0.219   |
| Pre HR    | 75.70 ± 13.14     | 74.20 ± 13.47       | 0.664   |
| HR 1 min  | 69.13 ± 12.65     | 66.06 ± 10.38       | 0.309   |
| HR 3 min  | 69.37 ± 12.50     | 67.56 ± 10.81       | 0.553   |
| HR 5 min  | 69.66 ± 12.67     | 66.03 ± 11.19       | 0.244   |
| HR 8 min  | 69.33 ± 11.32     | 65.66 ± 11.74       | 0.233   |
| HR 13 min | 68.66 ± 12.35     | 63.43 ± 10.63       | 0.084   |
| HR 18 min | 68.96 ± 11.61     | 62.56 ± 9.81        | 0.025   |
| HR 23 min | 61.37 ± 10.36     | 61.80 ± 9.49        | 0.929   |
| HR in LMA time | 75.72 ± 13.12 | 71.6 ± 9.83         | 0.176   |
| Pre MAP   | 111.32 ± 14.47    | 111.11 ± 14.87      | 0.956   |
| MAP 1 min | 88.67 ± 16.50     | 91.22 ± 20.43       | 0.598   |
| MAP 3 min | 85.30 ± 17.32     | 88.94 ± 18.56       | 0.461   |
| MAP 5 min | 83.52 ± 16.09     | 84.48 ± 18.74       | 0.831   |
| MAP 8 min | 83.84 ± 14.78     | 82.62 ± 15.34       | 0.755   |
| MAP 13 min| 80.11 ± 13.78     | 76.67 ± 12.81       | 0.322   |
| MAP 18 min| 81.91 ± 14.58     | 76.61 ± 12.25       | 0.133   |
| MAP 23 min| 84.75 ± 10.60     | 76.40 ± 9.09        | 0.091   |
| MAP in LMA time | 100.01 ± 11.76 | 100.48 ± 13.20     | 0.885   |
the selected correlation structure based on CEBIC and CEaic criteria was different when using traditional criteria such as CIC and QIC. As a result, the estimated effects of propofol and isoflurane on BIS, HR, and MAP and the relevant standard errors were affected during cataract surgery. In addition, competing candidate models have had different time effects on BIS, HR, and MAP.

Traditional model selection criteria, such as QIC, CIC, EAIC, and EBIC, are not suitable for cases of irregular observation timing (Wang and Fu 2017). The assumption of these criteria is that all subjects will share the same matrix of correlation that is not established in the presence of irregular observations (Chen and Lazar 2012). Due to the nature of the anesthesia and the different operating time, the data presented here were exposed to irregular time intervals during surgery. Khakzad et al. analyzed this dataset using repeated measures analysis of variance (RMANOVA) which considered the same time points and regular observation timing for each participant (Khakzad et al. 2019). RMANOVA works when complete observations are available for each participant. In the case of irregular time intervals, therefore, RMANOVA considers the minimum number of repeated observations and omits the remaining information. Omitting the observations causes an imbalance in baseline measurements between the two study groups and reduces the power of statistical tests.

The results of a simulation study conducted by Wang et al. showed that all criteria work well when the sample size is large (more than 60) (Wang and Fu 2017; Chen et al. 2018). The selection accuracy of all criteria increased as the size of the sample increased. In addition, CEAIC and CEBIC preferred the correct structure more than 74% of the time for all settings. The performance of CEAIC and CEBIC for unbalanced data was similar to that of balanced data. When the true correlation structure is the independence model, the CEBIC has higher selection accuracy than the CEAIC. The performance of CEAIC and CEBIC was the same when the correlation structure is exchangeable or AR (1). Additionally, CEAIC and CEBIC perform better than CIC and QIC, in particular for small sample sizes and large repeat measurements (e.g., sample size = 30 and repeated

| Table 3 | Results of fitting GEE model, EAIC, and EBIC criteria for BIS outcome |
|--------|------------------|------------------|------------------|------------------|
|        | Independent      | Exchangeable     | AR-1             | Unstructured     |
|        | B (SE)           | B (SE)           | B (SE)           | B (SE)           |
| Intercept | Ref | Ref | Ref | Ref |
| Propofol | 2.02 (3.83) | 1.95 (3.74) | 1.66 (4.38) | −0.81 (5.01) |
| Isoflurane | −0.64 (1.13) | −0.70 (1.16) | −0.64 (1.27) | −7.90 (2.39) |
| Time | −0.02 (0.71) | 0.007 (0.73) | 0.05 (0.80) | 1.18 (1.49) |
| Interaction (Isoflurane x time) | CEAIC | 395.77 | 417.88 | 2067.91 | 2081.79 |
| Time | 402.06 | 426.25 | 2076.29 | 2090.17 |
| CIC | 1.55 | 2.44 | 1.07 | 1.68 |
| QIC | 199,314.21 | 199,321.97 | 200,484.14 | 206,600.00 |

| Table 4 | Results of fitting GEE model, EAIC, and EBIC criteria for HR outcome |
|--------|------------------|------------------|------------------|------------------|
|        | Independent      | Exchangeable     | AR-1             | Unstructured     |
|        | B (SE)           | B (SE)           | B (SE)           | B (SE)           |
| Intercept | Ref | Ref | Ref | Ref |
| Propofol | −1.97 (2.29) | −1.54 (2.87) | −1.69 (3.40) | 0.03 (2.78) |
| Isoflurane | 0.16 (0.68) | 0.46 (0.38) | 0.52 (0.78) | 0.44 (0.42) |
| Time | −0.32 (0.43) | −0.47 (0.24) | −0.28 (0.49) | −0.50 (0.26) |
| Interaction (Isoflurane x time) | CEAIC | 524.98 | 38.77 | 23.99 | 9.43 |
| Time | 531.26 | 47.14 | 32.36 | 17.81 |
| CIC | 13.01 | 4.74 | 3.25 | 30.27 |
| QIC | 71,364.61 | 71,382.20 | 79,432.01 | 73,659.28 |

| Table 5 | Results of fitting GEE model, EAIC, and EBIC criteria for MAP outcome |
|--------|------------------|------------------|------------------|------------------|
|        | Independent      | Exchangeable     | AR-1             | Unstructured     |
|        | B (SE)           | B (SE)           | B (SE)           | B (SE)           |
| Intercept | Ref | Ref | Ref | Ref |
| Propofol | 2.36 (3.48) | 2.25 (3.87) | −0.42 (4.96) | 1.14 (3.51) |
| Isoflurane | −0.57 (1.03) | −0.59 (0.88) | −0.99 (1.33) | −0.29 (0.88) |
| Time | −0.61 (0.65) | −0.57 (0.55) | 0.04 (0.83) | −0.76 (0.55) |
| Interaction (Isoflurane x time) | CEAIC | 398.13 | 120.30 | 16.54 | 29.33 |
| Time | 404.41 | 128.68 | 24.92 | 37.71 |
| CIC | 7.32 | 3.74 | 2.06 | 11.27 |
| QIC | 164,048.44 | 164,046.69 | 179,358.87 | 170,433.62 |

*B (SE) estimation of regression coefficient (standard error)
measures = 10). In addition, it should be noted that CEAIC and CEBIC are more robust against the number of variables than CIC and QIC.

Eventually, although the GEE theory states that the average parameter estimates are consistent with any working correlation model, an important related issue is whether the selected candidate model is acceptable to the working correlation model, an important related issue is whether the selected candidate model is acceptable to the working correlation between the repeated measurements of anesthetic indices obtained during cataract surgery. In the future, it is necessary to analyze anesthetic data with irregular timing measurements and to compare the results with traditional criteria.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s42077-020-00086-7.

Additional file 1. The codes written in R software program for computing CEBIC and CEAIC after perform of GEE model.

Abbreviations

GEE: Generalized estimating equations; CEBIC: Constraint Empirical Bayesian Information Criterion; CEAIC: Constraint Empirical Akaike Information Criterion; CIC: Correlation information criterion; QIC: Quasi-likelihood information criterion; AR: Auto regressive; IWANOVA: Repeated measures analysis of variance; BIS: Bispectral index; OR: Odds ratio; MAP: Mean arterial pressure; HR: Heart rate

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Authors’ contributions

MC has made substantial contributions to the conception and design of the work; ZG and MC and SHS the acquisition, analysis; SMR and MKH interpretation of data; MC, ZG, SHS, SMR, and MKH have drafted the work or substantively revised it. MC, ZG, SHS, SMR, and MKH have approved the submitted version (and any substantially modified version that involves the author’s contribution to the study); and to have agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. ZG is responsible for ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors, and that all authors receive the submission and all substantive correspondence with editors, as well as the full reviews, verifying that all data, figures, materials (including reagents), and code, even those developed or provided by other authors, comply with the transparency and reproducibility standards of both the field and journal.

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Availability of data and materials

The data will be available for editors in case of reasonable requests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Babol University of Medical Sciences. Written informed consent was obtained directly from the participants.

Consent for publication

Not applicable

Competing interests

No authors have conflict of interest related with this.

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