Original Article

DOI: 10.7860/JCDR/2023/59761.17994

Statistics Section

Impact of Correlation between Multiple Time Point Measurements on Pooled Effect Measures in Meta-analysis

DEEPTHY MELEPURAKKAL SADANANDAN[1], N SREEKUMARAN NAIR[2], KT HARICHANDRAKUMAR[3]

ABSTRACT

Introduction: Effect estimates obtained from multiple time points based on the same set of subjects are observed to be correlated. There is a need to integrate these correlations in the derivation of pooled summary measures to improve the precision of estimates. The conventional meta-analysis does not consider this dependency into account.

Aim: To compare the results obtained from meta-analysis which incorporate various levels of correlation in repeated measures data to the traditional meta-analysis.

Materials and Methods: The present statistical analytical study was conducted at Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, from January 2021 to February 2022 on data from a systematic review that studied the effect of analgesics in reducing orthodontic pain using Visual Analogue Scale (VAS) pain score measured at three time points was used for demonstration. This study attempted to illustrate two distinct approaches to deal with dependency between measurements obtained from different follow-ups by adopting constant and degenerating correlation structures.

Results: The pooled effect estimates and confidence intervals obtained from models which incorporated correlation were different from the results of traditional approach. Naproxen fared to be better when compared to other two treatments. Pooled effect estimates and confidence intervals from Model 2 and Model 3 hovered around the same values. Non significant difference was observed in the Akaike Information Criterion (AIC) values of Model 2 and Model 3 for all three treatments. The between study variance ranged from 0.07 to 1.46, 1.25 to 3.17 and 0.01 to 0.98 for Acetaminophen, Naproxen and Ibuprofen, respectively.

Conclusion: The models which took care of dependency had a better fit to the data over conventional meta-analysis.

Keywords: Correlated effect estimates, General linear mixed model, Repeated measures, Visual analog scale score

INTRODUCTION

In healthcare research, outcomes are measured at different follow-ups times to monitor the health status of patients. It has been reported that the outcomes obtained in such a way as heart rate, VAS score and pulmonary function, Forced Expiratory Volume in the first second (FEV1) tend to be highly correlated across different time points [1-3]. Ignoring this stochastic dependency during the analysis will overestimate p-values for within-subject or within-cluster comparison and underestimate in between-subject or between-cluster comparison [4]. Diverse statistical techniques like paired t-test, Wilcoxon signed rank test, Mc-Nemar's test repeated measures Analysis of Variance (ANOVA), linear mixed models, generalised estimating equations etc. are used to address this dependency [5-7]. The effect estimates obtained from multiple time points in longitudinal studies may likewise be related since they are procured from the same set of study units. In the conventional meta-analytic approach, a separate meta-analysis is done for each time point without considering this correlation. Multivariate meta-analysis is an alternative which can model the dependent effect estimates [8]. Likewise, a meta-analysis of multiple time points can also be carried out in the General Linear Mixed (GLM) model framework which can account for correlation between time points [9-11].

This study has examined, whether the summary results and conclusions from the meta-analytic models of a set of data measured at multiple time points that incorporates dependency differ from the same data meta-analysed by ignoring dependency.

MATERIALS AND METHODS

This study was conducted at Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, from January 2021 to February 2022.

Procedure

Data source: The data for the present study was taken from a published systematic review that studied the efficacy of analgesics in controlling orthodontic pain: a systematic review and meta-analysis [12]. The study compared the efficacy of three different analgesics: ibuprofen, acetaminophen and naproxen on the relief of pain in orthodontic treatment compared to the placebo among patients with orthodontic pain. Change in VAS score measured at 2, 6 and 24 hours in different studies was chosen for the demonstration of meta-analysis of longitudinal studies. The effect size was the standardised difference in means.

STATISTICAL ANALYSIS

Meta-analytic framework for modeling covariance: The effect estimates from multiple time points were pooled through different models using the GLM model framework [11]. A more flexible unified modeling framework proposed by Sera F et al., was performed for a set of effect sizes measured at k_i times in study i as given below [11]:

$$y_{it} = (\theta + g_i) + (\gamma + h_i)t_{ij} + \varepsilon_{it}, i = 1,2,..m, j = 1,2..k_i,$$

$$[g_i + h_i] \sim N(0, \Psi), \left[\varepsilon_{it_1}, \ldots, \varepsilon_{it_{k_i}}\right] \sim N(0, S_i)$$

Where, θ, γ, g_i, and h_i are fixed and random effect coefficients for intercepts and slopes. Three different models were built by specifying combinations of three different variants of within study variance covariance structures like Independent, Heterogeneous Compound symmetry and Heteroscedastic autoregressive as given below:

Model 1: Independent random time effects model (Zero correlation): This model assumes the effect sizes to be independent

and will yield similar results to those of traditional univariate meta-analyses carried out for each time point separately. An independent variance covariance structure that assumes that zero correlations between the effect estimates obtained from any two time points was used.

Model 2: Correlated within study model with constant correlation: This model is an extension of Model 1, where dependency between effects estimates obtained from different time points are considered. However, this within study serial correlation between longitudinal effect sizes is assumed to be a constant. Compound symmetry variance covariance which assumes correlation to be the constant across any two time points was adopted. A moderate correlation (r=0.50) was assumed between any two time points in the current study.

Model 3: Correlated within study model with degenerating correlation: In this model, which is also again an extension of Model 1, dependency between effect estimates obtained at different time points are considered to be degenerating as duration increases. A heteroscedastic autoregressive variance covariance matrix in which the correlation exponentially decreases with an increase in the time lag between the time points was used. If the correlation between first and second time point was assumed to be 'r', then the correlation between first and third was assumed to be $r^{|3-1|}$. In the current study, a correlation of 0.50 was assumed between the first time point and second time point whereas the correlation diminished to 0.25 for the first and third time point. Likewise, the correlation between second and third was 0.50.

The between study variance covariance matrix was assumed to be independent in models 1, 2 and 3. The results were reported in terms of pooled effect estimates along with their 95% Confidence intervals (95% CI) for all three time points of interest. The results obtained from meta-analysis with the assumption of independence were compared to the models which incorporated the correlations. The change in the treatment effect estimates and their precisions were compared. The deviance measures like Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were calculated and compared across models to identify the best fitted model. A model with the lowest AIC or BIC values were considered to be a good fit for the data. All the analyses were carried out using mixmeta package in R software version 4.1.1 [13].

RESULTS

Among the included studies, there were six, four and nine trials studying the effectiveness of Acetaminophen, Naproxen and Ibuprofen treatments, respectively. The sample size of the trials ranged from 15 to 38, 17 to 30 and 10 to 41 for Acetaminophen, Naproxen and Ibuprofen treatment comparisons. The results obtained through GLM models which considered the correlation are given in [Table/Fig-1]. The usage of independent covariance structure (Model 1.) yielded the same results as those of the multiple univariate meta-analyses in case of all treatment comparisons. A higher reduction in the pain score was observed at six hours in Naproxen and Ibuprofen whereas the Acetaminophen showed the highest improvement after 24 hours. The reduction in pain score was observed to be almost same after 24 hours for the first two treatments, Acetaminophen and Naproxen. The trajectory of pain reduction was same over the period of time for the treatments, Naproxen and Ibuprofen.

A similar pattern of trend in the effect estimates across different time points was also found among the models which incorporated dependency. All the results were found to be statistically significant. Naproxen fared to be better when compared to other two treatments. The pooled effect estimates and confidence intervals obtained from models which incorporated correlation were different from the results of traditional approach. Pooled effect estimates and confidence intervals from Model 2 and Model 3 hovered around the same values [Table/Fig-2].

The AIC values of models which took care of the dependency into account were lesser when compared to the conventional method. No significant difference was observed in the AIC values of Model 2 and Model 3 for all three treatments. The between study variance ranged from 0.07 to 1.46, 1.25 to 3.17 and 0.01 to 0.98 for Acetaminophen, Naproxen and Ibuprofen, respectively.

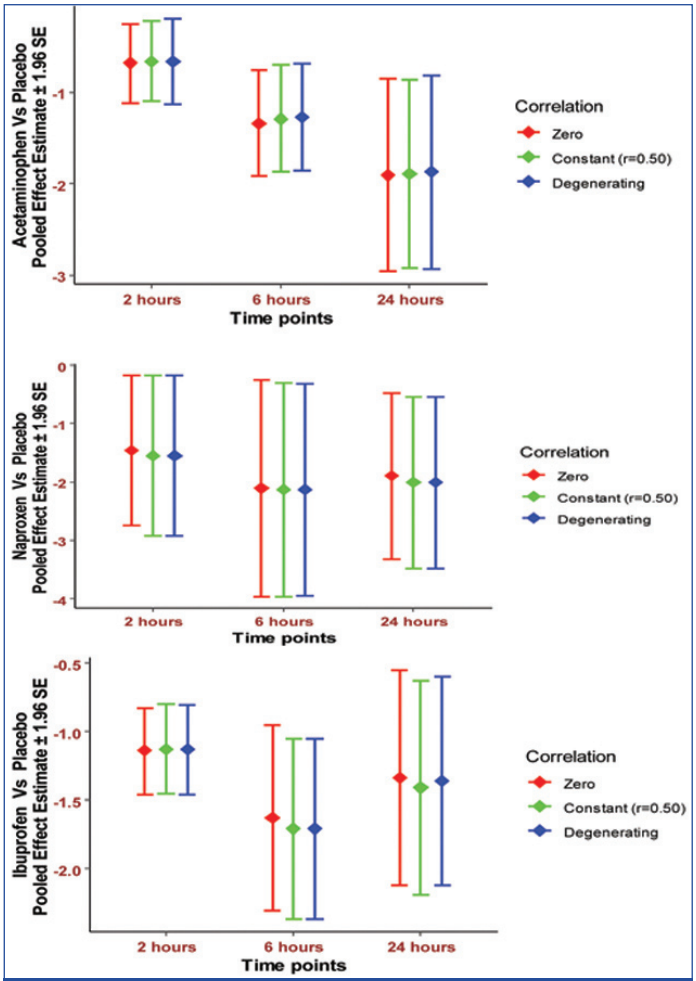
DISCUSSION

The present study has examined the impact of correlation between multiple time point measurements on pooled effect measures in meta-analysis. The models (model 2 & 3) which incorporated the dependency between time points gave substantially lesser AIC values when compared to model which didn't incorporate correlation (Model 1) indicating them to be better fit to the data. The pattern observed was same in case of all the treatment comparisons. This emphasises the need for considering the correlation structure existing between multiple time points.

Additionally, the current study proposed a constant correlation between the effect sizes across time points (Model 2) whereas the previous studies assumed a constant correlation between effect estimates across different studies [8-11]. Ishak KJ et al.,

Treatment comparison		Acetaminophen vs placebo			Naproxen vs placebo			Ibuprofen vs placebo		
Model		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Within-study errors (S_i)		Indep	HCS	HAR(1)	Indep	HCS	HAR(1)	Indep	HCS	HAR(1)
SMD (95% CI)	2 hours	-0.68 (-1.12,-0.25)	-0.66 (-1.10,-0.22)	-0.66 (-1.13,-0.19)	-1.46 (-2.75,-0.17)	-1.55 (-2.93,-0.17)	-1.55 (-2.92,-0.17)	-1.14 (-1.46,-0.83)	-1.13 (-1.45,-0.80)	-1.13 (-1.46 ,-0.81)
	6 hours	-1.34 (-1.92,-0.76)	-1.29 (-1.87,-0.70)	-1.27 (-1.86,-0.69)	-2.11 (-3.97,-0.25)	-2.13 (-3.96,-0.30)	-2.13 (-3.95,-0.32)	-1.63 (-2.31,-0.95)	-1.71 (-2.37,-1.05)	-1.71 (-2.37,-1.05)
	24 hours	-1.91 (-2.96,-0.85)	-1.89 (-2.92,-0.86)	-1.87 (-2.93,-0.81)	-1.90 (-3.32,-0.48)	-2.01 (-3.48,-0.55)	-2.01 (-3.48,-0.55)	-1.34 (-2.12,-0.55)	-1.41 (-2.19,-0.63)	-1.36 (-2.12,-0.60)
Between study variance estimate	2 hours	0.07	0.12	0.15	1.25	1.52	1.51	0.01	0.02	0.02
	6 hours	0.33	0.36	0.37	3.17	3.05	3.01	0.61	0.59	0.57
	24 hours	1.46	1.38	1.48	1.61	1.79	1.78	0.98	0.98	0.88
Model fit	AIC	46.74	36.01	37.31	45.15	32.24	32.67	78.18	75.51	75.53
	BIC	50.58	40.48	41.78	46.33	33.62	34.05	85.25	83.76	83.78

[Table/Fig-1]: Meta-analysis with linear mixed models under assumption of different levels of correlation between time points and standardised mean difference of VAS score between treatment vs. placebo measured at three different time points (2,6, 24 hours).
AIC: Akaike information criterion; BIC: Bayesian information criterion; CI: Confidence interval; SMD: Standardised mean difference; HAR(1): Heteroscedastic autoregressive (1); HCS: Heterogeneous compound symmetry; Indep: Independence; VAS score: Visual Analogue Scale pain score



[Table/Fig-2]: Comparison pooled effect estimates obtained through zero, constant and degenerating correlation for the treatment comparison: a) Acetaminophen vs. Placebo (6 trials); b) Naproxen and Placebo (4 trials); and c) Ibuprofen and Placebo (9 trials).

developed and compared several methods to handle correlations of longitudinal effect estimates in a meta-analysis using data on deep brain stimulation among patients with Parkinson's disease measured at various time points [9]. The outcome investigated was the Unified Parkinson Disease Rating Scale (UPDRS) motor function score, a continuous outcome. Three different models namely, study specific random effects, general multivariate method which can incorporate correlated within study residuals, and correlated time-specific random effects were used. The model that used the multivariate approach provided a better fit to the data than the other two models. The models that used inherent correlation provided more precise summary estimates. Methods that consider stochastic dependencies between effect estimates obtained from subsequent time points was developed by Trikalinos TA and Olkin I [8]. The outcome was survival rate at different follow-ups and the effect estimate used was the odds ratio. Different methods by assuming varying variance covariance structures were compared with univariate meta-analysis. Minor changes were observed in the magnitude of the effect sizes and their corresponding standard errors obtained from univariate and multivariate analyses. The study concluded that data acquired from multiple time points are multivariate in nature and therefore must be analysed using multivariate techniques.

Musekiwa A et al., compared five different GLM models by assuming different within and between variance covariance structures [10]. GLM models are more flexible and can easily take care of new combinations of covariance structures like heterogeneous compound symmetry, heteroscedastic autoregressive, independence etc. The models were demonstrated using the same survival data used for demonstration by Trikalinos TA and Olkin I [8]. The model which used a heteroscedastic autoregressive structure performed better. Joint analysis of correlated effect estimates using an autoregressive covariance structure provided more precise estimates when compared to the compound covariance structure. All five models that incorporated correlation fitted better to the data when compared to the traditional approach. Only Ishak KJ et al., described meta-analysis of longitudinal time points using continuous data whereas all the other studies used binary outcomes [9].

In this study, Model 3 which assumed heteroscedastic autoregressive was found to be better when compared to other models in previous studies [10,11]. Model 2 and model 3 which used heterogeneous compound symmetry and heteroscedastic autoregressive gave similar AIC values in the current study. This may be due to the more similarity in the correlation structure since there was fewer number of time points.

Under both meta-analysis with and without considering dependency, all three treatments were found to be better when compared to the placebo group at all the time points and the results were found to be statistically significant. However, there was a change in the magnitude of pooled effect estimate after incorporation of the correlation.

Intervention studies may produce an upward trend in effect estimates that may finally stabilise over a period of time, or they may cause effect estimates to plummet and revert to their baseline value. As a result, the effect measures either obtained from the subsequent time points will be more correlated as compared to those from the baseline and last time points. The changes brought to those time points after incorporating those correlations in the variance covariance structure can be closely observed depending upon the clinical significance.

Limitation(s)

One limitation of the current study was that, it didn't addressed the analysis of categorical outcome and adjusting for the effect of the covariate. Also, the number of time points were less in order to study the decay of correlation with time.

CONCLUSION(S)

It was observed that the correlation between the repeated measurements has an influence in the pooled effect estimates at different time points. Hence, deriving pooled effect estimates by incorporating correlation during meta-analysis of repeated measures data would be a better choice. The more flexible general framework incorporating the correlation may result in more valid estimates.

REFERENCES

[1] Albanese M, Neofytou M, Ouarrak T, Schneider S, Schöls W. Evaluation of heart rate measurements in clinical studies: a prospective cohort study in patients with heart disease. Eur J Clin Pharmacol. 2016;72(7):789-95.
[2] Karabis A, Nikolakopoulos S, Pandhi S, Papadimitropoulou K, Nixon R, Chaves RL, et al. High correlation of VAS pain scores after 2 and 6 weeks of treatment with VAS pain scores at 12 weeks in randomised controlled trials in rheumatoid arthritis and osteoarthritis: meta-analysis and implications. Arthritis Res Ther. 2016;18(1):73.
[3] Juwara L, Boateng J. Assessing the effects of exposure to sulfuric acid aerosol on respiratory function in adults [Internet]. arXiv; 2019 [cited 2022 Aug 20]. Available from: http://arxiv.org/abs/1906.04296
[4] Sainani K. The importance of accounting for correlated observations. PM&R. 2010;2(9):858-61.
[5] Schober P, Vetter TR. Repeated measures designs and analysis of longitudinal data: If at first you do not succeed-try, try again. Anesth. Analg. 2018;127(2):569-75.
[6] Davis CS. Statistical Methods for the Analysis of Repeated Measurements [Internet]. New York, NY: Springer; 2002 [cited 2022 Nov 30]. (Springer Texts in Statistics). Available from: https://link.springer.com/10.1007/b97287.
[7] Rana R, Singhal R, Singh V. Analysis of repeated measurement data in the clinical trials. J Ayurveda Integr Med. 2013;4(2):77.
[8] Trikalinos TA, Olkin I. Meta-analysis of effect sizes reported at multiple time points: A multivariate approach. Clin. Trials. 2012;9(5):610-20. Available from: http://journals.sagepub.com/doi/10.1177/1740774512453218.
[9] Ishak KJ, Platt RW, Joseph L, Hanley JA, Caro JJ. Meta-analysis of longitudinal studies. Clin. Trials. 2007;4(5):525-39. Available from: http://journals.sagepub.com/doi/10.1177/1740774507083567.

[10] Musekiwa A, Manda SOM, Mwambi HG, Chen DG. Meta-Analysis of effect sizes reported at multiple time points using general linear mixed model. Bagos PG, editor. PLoS ONE. 2016;11(10):e0164898.
[11] Sera F, Armstrong B, Blangiardo M, Gasparrini A. An extended mixed-effects framework for meta-analysis. Stat. Med. 2019;38(29):5429-44.
[12] Cheng C, Xie T, Wang J. The efficacy of analgesics in controlling orthodontic pain: A systematic review and meta-analysis. BMC Oral Health. 2020;20(1):259.
[13] Gasparrini A, Sera F. mixmeta: An extended mixed-effects framework for meta-analysis [Internet]. 2021 [cited 2022 Aug 20]. Available from: https://CRAN.R-project.org/package=mixmeta.

PARTICULARS OF CONTRIBUTORS:
1. Scholar (PhD), Department of Biostatistics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India.
2. Professor, Department of Biostatistics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India.
3. Assistant Professor, Department of Biostatistics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
N Sreekumaran Nair,
Professor, Department of Biostatistics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry-605006, India.
E-mail: nsknairmanipal@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 27, 2022
- Manual Googling: Dec 01, 2022
- iThenticate Software: Dec 14, 2023 (19%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 22, 2022**
Date of Peer Review: **Nov 26, 2022**
Date of Acceptance: **Dec 24, 2022**
Date of Publishing: **Jun 01, 2023**