Dependent Prior: An Application in Spinal Anaesthesia Drug Treatment Effect Comparison

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Abstract

Cesarean section is widely used operation procedure in the world. The regional anesthesia is preferred than general anesthesia. The risk of fetus is higher in general than in regional anesthesia. The drug treatment effect on regional anesthesia plays an important role to control the systolic blood pressure (SBP) during the surgery. The goal of this work is to know the effective drug to control the SBP among cesarean anesthetic patients. The dependent prior with Bayesian approach is applied in the binary response data set. The secondary data in anesthesia has been applied to compare the two drug treatments, viz. (1) Phenylephrine and (2) Ephedrine, in cesarean patients with spinal anesthesia. In both drug groups the mean of SBP has been found controlled over the duration of the surgery. No rapid changes of SBP level among the patients are observed. At the end of study it is found that the means of SBP cesarean anesthetic patients are found higher in Phenylephrine group. The Bayesian dependent prior is found to offer effective tool for drug treatment effect comparison. The drug treatment effect Ephedrine is found to be more effective to control the SBP over the duration of surgery than Phenylephrine.

Introduction

Now a day, cesarean section is well accepted and widely practiced operation procedure. The high private insurance rate, medical malpractice cost and age of mother are influencing factors for cesarean section (Chen et al,. (1999), Smith et al,. (2008), Sufang et al,. (2007) and Sreevidya et al,. (2003)). It can be stated that the general anesthesia is not in practice for cesarean operation. In case of emergency operation, general anesthesia is in front line than regional anesthesia. The maternal mortality is associated with general anaesthesia (Algert et al,. (2009), McDonnell et al,. (2008), and Enohumah et al,. (2006)). Risk of fetus is higher in general than regional anaesthesia. However, the spinal regional anesthesia is not free from side effects. The supine hypotension can be occurred as an effect of spinal anesthesia (Hanss et al,. (2007)). The spinal anaesthesia gives unique improvement in comparison to other regional anaesthesia (Tzovaras et al,. (2006), and Vaghadia et al,. (2001)). However, the spinal anaesthesia is not appropriate in Laproscopic surgery (Palace et al,. (2007) and Toda et al,., (1977)). The local anaesthetic in combination with clonidine can be useful to decrease shoulder tip pain (Poonam et al,. (2010)). The ephedrine, and phenylephrine is effective to control the combat maternal hypotension (Ngan et al,. (2007) Cooper (2007) and Erkinaro et al,. (2007)). In spinal Anesthesia, Ephedrine and Phredrine are most useful drug. Edgeworth (1930) has reported first about the effectiveness of ephedrine in 1930.

This paper is contributed to compare the effectiveness of ephedrine and phredrine to control the SBP. The dependent prior with Bayesian approach is explored to compare drug treatment effect in patients data observed during anaesthsia with cesarean surgery.

Data Methodology

The treatment effect of anaesthesia was considered in this study. A total of 60 patients were randomized to each treatment group and followed over duration of 25 minutes. The measurements of clinical parameters were observed at different point of time. The partial data set with the measurement of SBP observation was considered in this work. Participants in this study were allocated to either of two anaesthesia drug (denoted treatment 1for ephedrine and treatment 2 for phredrine). The effects on SBP were compared through the application of dependent prior and Bayesian Odds ratio. The SBP observations were categorized to (1) more than a normal and (2) less than the normal range in the binary form (e.g. Ovbiagele et al,. (2011)). The SBP was considered as the measures of hypotension among cesarean operated patients. The observations of each patient were measured at minutes $2(t_1)$,$4(t_2)$,$6(t_3)$,$8(t_4)$,$10(t_5)$,$12(t_6)$,$14(t_7)$,$16(t_8)$,$18(t_9)$, $20(t_{10})$ and $25(t_{11})$ respectively. The measurement of SBP was categorized into two by less than and above normal range. The categorized and comparable drug treatment effects were tabulated. Table 1, a 2X2 contingency table is from the descriptive statistics of this randomized clinical trial on the relationship between types of treatment for an anesthesia and reduction of SBP level at the end of the 25 minutes are provided. No significant difference is observed among both the treatment.

Model

The outcome of interest in contingency table can be denoted by (X,Y). Here, the terms X and Y are used for type of treatment and level of SBP respectively. The joint probability distribution of (X,Y) can be observed through $\{\pi_{ij}\}$. The term π_{ij} represents the measurements of the i^{th} row and j^{th} column. The marginal distribution of row and column can be figured out through sum over the joint distribution function. The term π_{i+} and π_{+j} are assumed for the row variable and column variable by $\pi_{i+}=\sum_j \pi_{ij}$ and $\pi_{+j}=\sum_i \pi_{ij}$. In many cases it can be found that the two variables are response and independent. In those cases the conditional distribution of given X relates to the joint distribution is

$$\pi_{i/i}= \pi_{ij}/ \pi_{i+} \text{ for i and j.} \quad (1)$$

It becomes equal to the product of marginal probability. i.e. $\pi_{i+ \text{ and }} \pi_{+j.}$ In this particular case, the equation (1) can be extended by

$$\pi_{j/i=} \pi_{ij}/ \pi_{i+} . = \pi_{i+} \pi_{+j/} \pi_{i+=} \pi_{+j.} \quad (2)$$

In medical research, the comparison between two proportions plays an important role. The comparison concludes that one groups of treatment is better than other one with some degree of power. The comparison of failure can be considered as equivalent to the comparison of success since,

$$(1-\pi_1)-(1- \pi_2)= \pi_2- \pi_1=\theta;-1\leq\theta\leq1 \quad (3)$$

where, π_1 and π_2 represents success rate of treatment1 and treatment 2 respectively. The level of success and failure can be measured by odds ratio.

The term $\frac{\pi_1}{1-\pi_1}$ and $\frac{\pi_2}{1-\pi_2}$ can be applied as measure of odds of success in group one and two respectively.

The odds ratio (OR) becomes to

$$OR = \frac{\frac{\pi_1}{1-\pi_1}}{\frac{\pi_2}{1-\pi_2}} = \frac{\pi_1(1-\pi_1)}{\pi_2(1-\pi_2)} \tag{4}$$

The details of application of odds ratio can be cited with Agresti (2002).

In this work, the OR has been obtained through the prior assumption of the probability distribution in terms π_1 and π_2. The posterior mean has been used to compute the OR.

The contingency table 1 has been formulated with the cell frequency a,b,c,d. where, the success for the treatment 1 and treatment 2 can be measured by $\frac{a}{n}$ and $\frac{c}{n}$ respectively. In classical approach, the null hypothesis should be $p_1=p_2$. However, in this work, the precise hypothesis has been avoided. The sample space of P is estimated through $\widehat{P} = (\widehat{p_1}, \widehat{p_2})$; where$p_1 = \frac{a}{n}$ and $p_2 = \frac{c}{n}$ are the observed success in the two sample. The comparison between p_1 and p_2 is observed with,

$$l(p_1, p_2) = {p_1}^a(1-p_1)^b{p_2}^c(1-p_2)^d \tag{5}$$

The estimated value of a,b,c,d are obtained through sample observation of a,b,c and d respectively.

The Hypothesis H_1, has been fixed for $p_1>p_2$ and the correspondence evidence of probability computed with

$$\frac{\int_{p1=0}^{1}\int_{p2=0}^{p1} l(p_1, p_2)dp_2dp_1}{\int_{p1=0}^{1}\int_{p2=0}^{1} l(p_1, p_2)dp_2dp_1} \tag{6}$$

The details about the conditional and unconditional discussion about the contingency table can be cited with Berger et al,. (1997) and Little (1989).The statistical inference has been obtained through the iteration procedure of the sample value of this clinical trial,. The joint density function of p_1 and p_2 can be formulated with $f(p_1,p_2)$ by the observed posterior probability ($p_1>p_2$) with

$$\frac{\int_{p1=0}^{1}\int_{p2}^{p1} {p_1}^a(1-p_1)^b{p_2}^c(1-p_2)^d f(p_1, p_2)dp_2dp_1}{\int_{p1=0}^{1}\int_{p2}^{1} {p_1}^a(1-p_1)^b{p_2}^c(1-p_2)^d f(p_1, p_2)dp_2dp_1} \tag{7}$$

The joint function in equation (7) can be replaced by considering independent Haldane prior (Lane et al,. (1983)). Then the equation (7) becomes to,

$$k\frac{\int_{p_1=0}^{1}\int_{p_2=0}^{p_1} p_1^{a-1}(1-p_1)^{b-1}p_2^{c-1}(1-p_2)^{d-1}dp_2dp_1}{\int_{p_1=0}^{1}\int_{p_2}^{1} p_1^{a-1}(1-p_1)^{b-1}p_2^{c-1}(1-p_2)^{d-1}dp_2dp_1} = \frac{1}{B(a,b)(c,d)}\int_{x=0}^{1}\int_{y=0}^{x} x^{a-1}(1-x)^{b-1}y^{c-1}(1-y)^{d-1}dydx \tag{8}$$

For a,b,c,d>0 where B(a,b) and B(c,d) with Beta function.

Howard (1998) has discussed the application of dependent prior. It can be pointed that the dependent prior can solve many purposes in applied statistics. The application of dependent prior has been found very limited in the scientific literature. The performance of posterior likelihood of two independent proportions between Haldane and Jeffreys's prior can be given by

$$f(p_1, p_2) \propto p_1^{-1}(1-p_1)^{-1}p_2^{-1}(1-p_2)^{-1} \tag{9}$$

where, $f(p_1, p_2)$ are the joint density function of the two independent proportions p_1 and p_2.

The log-odds link function has been applied to measure the dependence between two proportions by

$$\theta_1 = In\left(\frac{p_1}{1-p_1}\right) \text{ and } \theta_2 = In\left(\frac{p_2}{1-p_2}\right). \tag{10}$$

The terms have been assumed to independent with uniform distribution $(-\infty, \infty)$.

The terms in the equation (1) has been generalized to the proportion of equation (3) by

$$e-\left(\frac{1}{2}\right)^{u^2} p_1^{\alpha-1}(1-p_1)^{\beta-1}p_2^{\gamma-1}(1-p_2)^{\delta-1} \tag{11}$$

where,

$$u = \frac{1}{\sigma} In\left(\frac{p_1(1-p_2)}{p_2(1-p_1)}\right) \tag{12}$$

Howard (1998) has preferred to use $\alpha = \beta = \gamma = \delta = 0$ and σ=1 as vegue prior. The stated model is applied in the SBP observation of the patients randomized into two treatments for anesthesia. The observation of SBP of each 2 minutes intervals are compared with initial observation of SBP. The total SBP of each patients are captured with 2,4,6,8,10,12,14,16,18 and 20 and 25 minutes respectively. The comparison of proportion of success of treatment at 4(t_2), 6(t_3), 8(t_4), 10(t_5), 12(t_6), 14(t_7), 16(t_8), 18(t_9), 20(t_{10}) and 25(t_{11}) minutes are compared with initial observation of SBP taken at 2(t_1) minutes respectively. The normal range of SBP is below 120. The value of SBP less than 120 is considered as success of treatment at any time.

Analysis

In this analysis the normal range of the SBP has been considered with 119 to 90 .The SBP value of an individual less than 120 in any times of reading has been coded by 1 other wise 0. For example, the SBP of i^{th} individuals t^{th} time reading with less than 120 value has been represented by $P(t_{ti}=1)$.whereas, more than or equal to 120 has been assumed with $P(t_{ti}=0)$.

We have formulated the odds ratio through

$$OR = \frac{P(t_2=1|t_1=1)P(t_2=1|t_1=0)}{P(t_2=0|t_1=1)P(t_2=0|t_1=0)} \tag{13}$$

where,

$P(t_2=1|\ t_1=1)$= Probability of individuals whose SBP are found less than 120 in the t_2^{th} time reading among those patients of normal level of SBP at the t_1^{th} time reading.

$P(t_2=1|\ t_1=0)$= Probability of individuals whose SBP are found less than 120 in the t_2^{th} time reading among those patients of above normal level of SBP at the t_1^{th} time reading.

$P(t_2=0|\ t_1=1)$= Probability of individuals whose SBP are found more than 120 in the t_2^{th} time reading among those patients of above normal level of SBP at the t_1^{th} time reading.

$P(t_2=0|t_1=0)$= Probability of individuals whose SBP are found more than 120 in the t_2^{th} time reading among those patients of above normal level of SBP at the t_1^{th} time reading.

The computed values of odds ratio's posterior mean are given in Table 2. The success of treatment at time i and j are presented as p_i and p_j. The analysis is performed to compare the probability of success by $p_i>p_j$. In table 2, $p_i = 0$ is used as the probability of success at time 0 and $p_j, j = 1,2,3,4,5,6,7,8,9,10)$ as the success rate in follow up observations.

Results and Discussion

The mean SBP levels in course of operation are shown in Table 2. In both the drug groups the mean of SBP was found controlled over the duration of the surgery. In both the group no rapid change of SBP level among the patients were observed. At the end of study, the mean (117.53) SBP in Phenylephrine treated patients was found higher than Ephedrine with (116.23). In the, 2^{nd} and the 3^{rd} minutes the $p_1>p_2$ were found 0.05 and 0.06 in comparison to 1^{st} minutes SBP level respectively. However, the same result was found in case of ephedrine by in minutes 2^{nd} and 3^{rd} with respect to 1^{st} minutes (Table 2). The ephedrine drug treatment was produced the posterior mean of odds ratio with 0.63(0.37) and 0.63(0.34) in the 2^{nd} and 3^{rd} visits in with respect to 1^{st} visits SBP level. The Odds ratio reveals the posterior mean for phenydrine drug by 0.68(0.37) and 0.5(.25) for the 2^{nd} and 3^{rd} visits. A small increase in the $p_i>p_j$ was observed in Phenylephrine drug group than Ephedrine group over the follow-up periods (Figure 1). It can be concluded that dependent prior with certain assumption produce comparative SBP figure with respect to study enrolment levels.

Hwang et al,. (1992) discussed the accuracy of hypothesis test with emerging properties of p-value. In this context, Nath and Bhattacharjee (2012), Bhattacharjee (2013), Evans (1994) and Robert et al,. (1996) explained the utility of Bayesian for hypothesis testing. Berger et al,. (1997) criticized the application of p-value and appreciated the application of Bayesian approach with precise Hypothesis. The theoretical extensions and discussions in this area are quite enriched in comparison to application. This work is focused to illustrate the application of Bayesian approach on precise hypothesis testing for drug trial effect comparison. In recent years, the biostatistics particularly the clinical trial is forced to enrich the theoretical filed of statistics. The bridge between applications of dependent prior with theoretical extension in clinical trial is neglected area. An alternative and unavoidable method like P-value is considered by several authors. Although, it is criticized by many authors (Bernardo (1980), Hwang et al,. (1992) and

Bhattacharjee (2013)).In this paper, our focus is to compare two treatment effects to control the SBP level in cesarean patients in India population. This slice of work provides an application tool to the observed the dependent longitudinal observations in clinical trials. Ephedrine is found to control SBP level in comparison to Phenylephrine. Gunda et al,. (2010) reported the spinal anehthesia is associated with hypotension. Magalhaes et al,. (2009) confirmed the occurrence of reactive hypertension and bradycardia as drug treatment of ephedrine and Phenylephrine. In this contrast, Loughrey et al,. (2002) found zero cases of rebound hypertension by ephedrine. Gunda et al., (2010) obtained the incidence of nausea and vomiting higher in ephedrine in comparison to phenylephrine drug treatment effect in Indian population. Kansal et al,. (2005), Macarthur et al,. (2007) and Loughrey et al,. (2002) also found that the elevated incidence of vomiting in ephedrine group. This study is only focused to compare the SBP levels among cesarean patients. Cleary et al,. (2005) reported that the ephedrine can raised the blood pressure by releasing the nonrepinephrine. The prophylactic ephedrine can be used to prevent the maternal hypotension and fetal late decelerations. The ephedrine is associated with fetal tachycardia. Gunda et al,. (2010) found the higher level of SBP in Phenylephrine as compared to ephedrine group. In this, the higher level of SBP is obtained in Phenylephrine group. There are several well documented studies proposed to prescribe the ephedrine than Phenylephrine (Erkinaro et al,. (2007), Erkinaro et al,. (2006) and Ralston et al,. (1974)). In this study, the ephedrine has been found better to control hypotension.

Conclusion

A novel method to compare the SBP level in cesarean patients and, therefore, the drug effect comparison of anaethesia is presented. The conclusion can be robust and easier to interpret with dependent prior. In clinical trial the 2X2 contingency table is widely used and unavoidable. The application of dependent prior can be looked as observable difference in results. However, it is advisable to exclude the hypothesis with application of dependent prior where $p_1=p_2$.Our results shows that the dependent prior can be considered for longitudinal data analysis and, consequently, for the actual application to the drug effect comparison in clinical trial,. The work has incorporated in R software to effectively compare the change of SBP levels drug surgery time in cesarean patients. The odds ratio has also been used with prior distribution in the drug treatment effect comparison. It can be confirmed that the dependent prior can be widely used in clinical trial,. The applied method can be considered in Clinical trial problems particularly in 2X2 contingency tables. The drug treatment effect of Ephedrine has been found more effective to control the SBP over the duration of surgery than Phenylephrine. The work is explored with prior distribution assumption through the posterior mean comparisons in cesarean patients. The application of dependent prior in contingency table can be considered as an alternative of the exact test with classical approach. It can be useful in 2X2 contingency table suitably.

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Table1: Cross-classification of Anesthesia Drug use and Reduction of SBP level at the end of 25 minutes of surgery

Type of Treatment	Below<120	Above ≥120	Total
Treatment1	17	13	30
Treatment2	18	12	30
Total	35	25	60

Table 2: Computed and comparable figure of Odds Ratio in follow-up observation of SBP

	SBP	Success	Failure	Posterior Mean of OR	SD	$p_i > p_j$
Treatment1	$t_2$vs t_1	20	10	0.63	0.34	0.05
Treatment2		20	10	0.68	0.37	0.06
Treatment1	$t_3$vs t_1	16	14	0.63	0.34	0.03
Treatment2		15	15	0.50	0.25	0.08
Treatment1	$t_4$vs t_1	16	14	0.21	0.15	0.01
Treatment2		15	15	0.20	0.14	0.32
Treatment1	$t_5$vs t_1	16	14	0.12	0.10	0.01
Treatment2		15	15	1.04	0.61	0.32
Treatment1	$t_6$vs t_1	16	14	0.20	0.14	0.39
Treatment2		15	15	2.11	1.29	0.23
Treatment1	$t_7$vs t_1	16	14	0.13	0.12	0.23
Treatment2		15	15	1.77	1.08	0.38
Treatment1	$t_8$vs t_1	16	14	0.29	0.19	0.20
Treatment2		15	15	1.60	0.96	0.24
Treatment1	$t_9$vs t_1	16	14	0.31	0.22	0.31
Treatment2		15	15	1.32	0.86	0.35
Treatment1	t_{10}vs t_1	16	14	0.20	0.14	0.44
Treatment2		15	15	1.32	0.78	0.48
Treatment1	t_{11}vs t_1	16	14	0.44	0.26	0.30
Treatment2		15	15	0.82	0.14	0.68

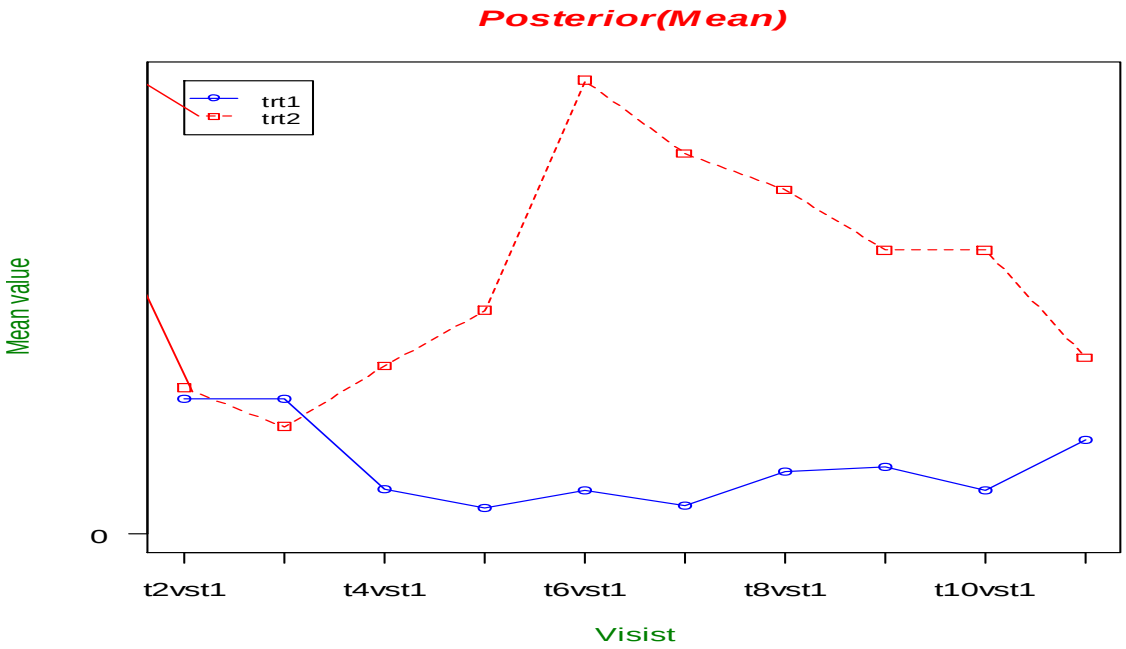

Figure 1: The posterior mean SBP value in follow up observation in treatment 1 and treatment 2.

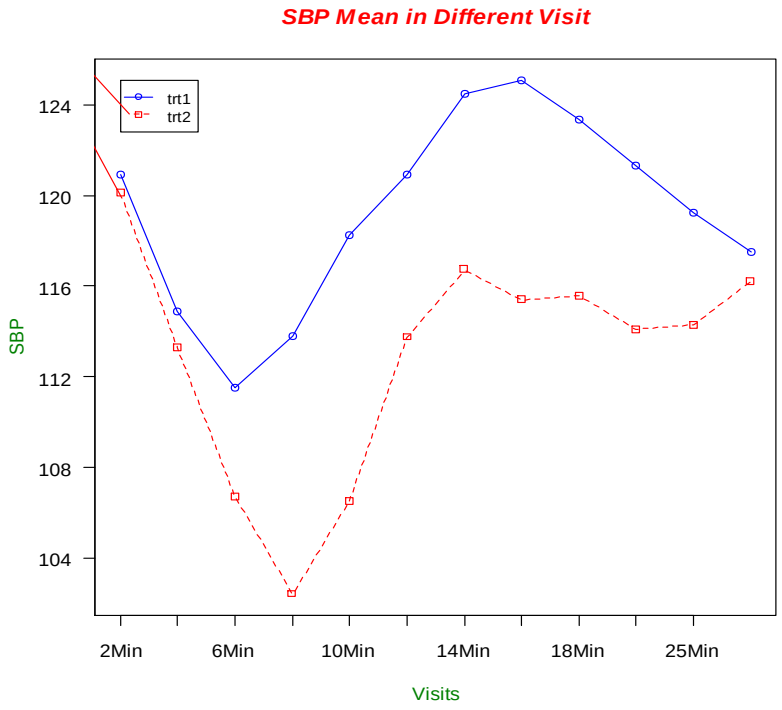

Figure 3: Mean of SBP in follow up observation in treatment 1 and treatment 2.