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Randomized Method for Dose Response Study Permuted Block by Block Randomization

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Abstract

Randomization is necessary for reducing bias in clinical studies, especially confirmatory studies. Since the 1970s, researchers proposed various methods of randomization. This has resulted in randomization becoming one of the most effective methods for bias control in clinical studies. Zelen proposed the importance of randomization and applied the permuted block randomization to a clinical study. After his work, Efron proposed the biased coin design in order to balance treatment assignments. Using Efron's biased coin design; the probability of assignment to the other group is constant, regardless of the degree of imbalance. Wei developed an adaptive biased coin design where the probabilities of assignment adapt according to the degree of imbalance. Despite the value of these randomization methods, the permuted block randomization is the preferred method used in clinical studies. This permuted block method is simple and easily controls the randomization of equal numbers of patients into each treatment group at each center. But the permuted randomization method has some shortcomings, one of which is predicting the allocation as it nears the end of block. This predictability of allocation induces some biases, especially selection bias. Increasing the block size leads to a lower predictability. However, increasing the block size is difficult in studies which includes several treatment groups because a large number of patients have to be randomized at each center. This causes incomplete randomization in several of the centers. Therefore, we propose the following method for improving permuted block randomization.

Keywords: Randomization; Permuted block randomization; Dose response study; Permuted block by block randomization; Relative efficiency

Introduction

The randomized controlled multicenter study sets the highest standard for clinical research. Random allocation by blocks, with regards to permuted block randomization, is frequently used to balance the number of patients in each treatment group in randomized controlled studies [1]. Permuted Block (PB) randomization has several valuable properties [2]. First, investigators can easily control an equal number of randomized patients into each treatment group in their centers. Investigators can assess all treatment groups set in the study, leading to a reduced center effect on treatment assessment. In other words, if only one treatment group is randomized and evaluated in a center, the assessment by the investigator in this center is reflected in the one treatment group, which causes the center effect. Second, unrestricted randomizations can result in severe imbalances at some point during the study. This is particularly undesirable if there is a time-heterogonous covariate related to treatment outcome, because imbalances in treatment assignments can then lead to imbalances in those important covariates. To avoid this, PB randomization is often used to ensure balance throughout the course of the clinical study. Third, the randomized procedures are easier than some adaptive randomization proposed by Efron [3] or Wei [4-7]. Finally, the logistics (preparation of investigational drugs, generation of allocation codes, and supply of investigational drugs to each center) are simple.

In spite of these properties, the PB randomization has some shortcomings. One of the critical limitations of PB randomization is that it is possible to predict the treatment situated at the end of a block when the block length is known [8]. Lack of concealment of allocation can invite selection bias, which is the preferential enrollment of specific patients into one treatment group over another [9].

One of the solutions for this is to increase block size. When a block size is two in a study setting two treatments, the second randomized patient is sure to take the different drug from the first randomized patient. If a block size is four, then the second randomized patient has a possibility of being allocated the same drug (0.333) or the different drug (0.667). The probability of allocating the second randomized patient to either drug converges to 0.5 as the block size increases. This solution works in confirmatory studies, which basically compare a new drug with a standard drug or a placebo. These studies usually set two treatment groups, meaning the new drug, and the standard drug, or placebo.

However, several doses of an investigational drug are evaluated in most clinical studies during new drug development. The safety profile of a drug is evaluated by setting more than five doses in a phase I study. At least three doses and placebo are also included in a dose response study in order to investigate the dose response relationship. If a PB randomization is applied to a dose response study, which includes at least four treatment groups, the smallest block size are often

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four. In this case it is difficult to increase the block size since some investigators cannot enroll large numbers of patients in their centers. This causes the randomized number of patients to be imbalanced among treatment groups if enrollments cannot fulfill block sizes.

In general, the same number of patients is randomized into each group at each center participating in a clinical study in order to adjust the effect of the center. Additionally, the investigator at each center seeks to randomize patients into all treatment groups because the imbalance interferes with the relationship between patient and investigator, especially all randomized patients given placebo in a center.

In this paper, we propose the method for reducing the predictability in PB randomization. First, our proposed method is explained in method. Next, the imbalance produced by our proposed method was assessed by formula and simulations, and the results of those simulations are shown in results. In motivating data, an application of this method to an actual study is illustrated. Finally, the results will be discussed.

Method

Our proposed method is illustrated in this Section. A study which includes several dose groups is assumed to be conducted for investigating the dose response relationship (dose response study). Suppose that the Low dose (L), Middle dose (M), High dose (H), and Placebo group (P) are set as treatment groups in a dose responsible study.

Generation of matrix

First, a matrix of each block is generated by the permuted block method [10]. L, M, and H are used as drug codes when the matrix is generated. The block size is then set at three. Therefore, there are the following six combinations. One of the six combinations is repeatedly sampled n times with a replacement. An n by three matrixes, called Matrix 1 (Mat1) is generated after replications.

LMH, LHM, MLH, MHL, HLM, HML

Next, a matrix which determines the change from active to placebo is also generated by the permuted block method. For this matrix the block size is set at four. This matrix includes three active dose codes (L, M, and H) and a "Stay (S)" code. "Stay" stands for "No change". Then, 24 combinations are generated (parts of these are shown below). One of the 24 combinations is repeatedly sampled m times with a replacement, where 4m equals n.

An one by n matrixes, called Matrix 2 (Mat2) is generated after replications.

LMHS, LHSM, …, SHML

This Mat2 is transposed. Mat2 is changed to a 4m by one matrix, or in other words, an n by one matrix. Then, Mat1 and Mat2 are matched for each block as shown in Table 1. If the same code exists in a block, for example, L exists in Mat1 and Mat2 in Block 1 of Table 1, and then L is changed to P. In other words, P, M, and H are allocated in order. If S exists in Mat2, Block 4 of Table 1, for example, then no code is changed. The new n by three matrixes is generated after this procedure is applied to all blocks (Table 2). Patients will be randomized into each treatment group according to this new matrix. Matching two matrices generated by the PB randomization twice provides the new matrix which is used for the randomization. Therefore, for the rest of this paper, our proposed method will be referred to as permuted block by block randomization.

Table 1: Match of matrix 1 to matrix 2.

Block	Mat1	Mat2
1	LMH	L
2	LHM	M
3	MLH	H
4	MHL	S
5	HLM	S
6	HML	H
7	LHM	M
8	HLM	L
.	…	.
n	LMH	S

Table 2: Randomization matrix.

Block	
1	PMH
2	LHP
3	MLP
4	MHL
5	HLM
6	PML
7	LHP
8	HPM
.	…
n	LMH

Extent for generation of matrix

The Mat1 is generated by the PB method with block size p-1, where p is the number of treatment groups set in a clinical study. Next, the Mat2 including p codes is also generated by the PB method. After the Mat2 is transposed, Mat1 and Mat2 are matched for each block. If the same code exists in a block, then that code is changed to placebo. This procedure is applied to all blocks. The newly generated matrix is used for randomization.

Assessment of permuted block by block randomization

The ratio of the largest number of randomized patients into a group to the smallest number of randomized patients into a group (RI) is calculated to assess the balance of randomization. It shows the imbalance indicator and ranges from zero to one. Patients are equally randomized into each treatment group if this ratio equals one. On the other hand, the number of randomized patients among treatment groups is biased as RI converges to zero. RI is also the relative efficiency when the pair wise comparison is made among treatment groups [11].

RI can be calculated by formula and simulation. Investigators often cannot enroll the number of patients which fulfills the block size at their centers. Supposing this case, some assumptions for incomplete situations are needed to calculate RI. Therefore, RI is

Table 3: Relative efficiency at the number of blocks.

Number of block (n)	Total number of randomization	Randomized numbers in each group: smallest / largest	RI
4	12	3 / 3	1.00
5	15	3 / 4	0.75
6	18	4 / 5	0.80
7	21	5 / 6	0.83
8	24	6 / 6	1.00
9	27	6 / 7	0.85
10	30	7 / 8	0.88
11	33	8 / 9	0.89
12	36	9 / 9	1.00
…	…	…	…

assessed by simulation in case of the incomplete randomization into block size.

The number of randomized patients in each group is determined. Then, B matrices are generated by replicating the procedures described in Generation of matrix, B times, where B is the number of simulation. RI is calculated at each matrix and assessed.

Results

The clinical study which includes three treatment groups and a placebo group was assumed to be conducted to show the dose response relationship. The method of generating the matrix was illustrated in Generation of matrix. The Mat1 was generated by the permuted block method with block size three. Then, the Mat2, which determined the changing code to placebo, was also generated by the PB method with block size four. Two matrices were matched after the transposition of Mat2. The matched code in each block was changed to placebo. The matrix for randomization was completed. And the assessment of permuted block by block randomization was done based on the RI described in Assessment of permuted block by block randomization.

Complete randomization into block size in each center

RI can be theoretically assessed in the case of complete randomization into block size in each center. The same number is randomized in each group at every four blocks in the matrix, for example, three patients are randomized in each of four groups when the number of block size for Mat2 is four. In general, there are four cases based on the odd of n, where n is a number of block. In the case that n is equal to multiples of four, RI is sure to be one because all randomized numbers in each group are the same.

In the case that n equals multiples of four plus one, the randomized number of a treatment group is one more than other treatment groups.

In the case that n equals to multiples of four plus two, the randomized number of two treatment groups are one less than others.

In the case that n equals to multiples of four plus three, the randomized number of a treatment group is one more than others.

Therefore, RI is calculated by the following formula:

$$RI = 1 \qquad \text{if } n = \text{multiple of } 4$$

$$RI = (n - 1 - \text{integer } [n/4]) / (n - \text{integer } [n/4]) \qquad \text{otherwise}$$

where integer [a] is the integer part of a. For example, integer [6.4] = 6.

Table 3 shows the part of the relationship between n and RI. The number of blocks, n is larger than 11, says total number of randomization is 33, then RI is larger than 0.9 in the permuted block by block method.

Incomplete randomization into block size in each center

In the case of incomplete randomization into block size in each center, some assumptions for incomplete situations are needed to calculate RI. Therefore, RI is assessed by simulation. RIs for two approaches, the PB method proposed by Zelen [1] and the PB method employed different sized blocks proposed by Schulz [12], were calculated in order to compare with the RI for the permuted block by block method. The replication of matrix generation was 10000 times (B in Assessment of permuted block by block randomization).

First, suppose that 240 patients were equally randomized into four treatment groups in a study. And one block was assumed to be assigned in each center. It means that four patients were sure to be randomized in each center in the case that the block size was four. A total of 60 centers would be needed if all centers randomized one block size (four patients). But if all centers randomized only three patients in each center, 80 centers would be needed. RIs in the permuted block by block method and the PB method were calculated by simulation. The RI was 1.0000 in the permuted block by block method (1 in Table 4). On the other hand, the mean value of RI was 0.8617 in the PB (6 in Table 4). As the block size was three in the permuted block by block method, RI was absolutely 1.0000. The smaller block size is one of the benefits of the randomization because the probability of complete randomization increases.

In case that 50% of participating centers were assumed to randomize one patient less than full block and 50% of participating centers were assumed to randomize two patients less than full block, the mean value of RI was 0.8962 in the permuted block by block method (2 in Table 4). In the case that 50% of participating centers were assumed to randomize one patient less than full block and 50% of participating centers were assumed to randomize two patients less than full block, the mean value of RI was 0.8990 in the PB method (7 Table 4).

Table 4: RIs of permuted block by block method (B by B), permuted block method (Permuted), and permuted block method employed different sized blocks (Different).

Method	N( )	Minimum	Mean	Median	Maximum
1) B by B	3 (80)	1.0000	1.0000	1.0000	1.0000
2) B by B	2 (48), 3 (48)	0.7536	0.8962	0.9032	1.0000
3) B by B	2 (27), 3 (62)	0.8154	0.9250	0.9206	1.0000
4) B by B	3 (40), 6(20)	1.0000	1.0000	1.0000	1.0000
5) B by B	2 (30), 3 (40), 6 (10)	0.8136	0.9255	0.9298	1.0000
6) Permuted	3 (80)	0.6571	0.8617	0.8636	1.0000
7) Permuted	3 (40), 4 (30)	0.7429	0.8990	0.9048	1.0000
8) Permuted	3 (20), 4 (45)	0.8281	0.9267	0.9355	1.0000
9) Permuted	2 (60), 4 (30)	0.7250	0.8781	0.8800	0.9718
10) Different	4 (30), 6 (20)	0.7313	0.9056	0.9048	1.0000
11) Different	3 (20), 4 (30), 6 (10)	0.7538	0.8958	0.9048	1.0000

N ( ): number of randomized patients into each group (number of centers)
No. of simulation: 10000

If centers which randomize two patients less than full block were occupied around 30% of total number of centers and the remaining centers were assumed to randomize one patient less than full block, the mean values of RI became 0.9250 in the permuted block by block method (3 in Table 4). If centers which randomize one patient less than full block were occupied around 30% of total number of centers, the mean values of RI became 0.9267 in the PB method, (8 in Table 4).

In the case that 20 centers were assumed to randomize six patients, the RI of the PB by block method would be compared with that of the PB method employed for different sized blocks. The PB method employing different sized blocks was reported to more equally randomize patients than the permuted method in this case [12]. The mean values of RI were 1.0000 in the permuted block by block method and 0.9056 in the permuted method employing different sized blocks, respectively (4 and 10 in Table 4).

In the similar profile of randomization in all centers (5 and 11 in Table 4), the mean values of RI were 0.9255 in the permuted block by block method and 0.8958 in the permuted method employing different sized blocks, respectively.

RIs showed 0.7536 to 1.0000 in the PB block by block method by simulation. These figures were comparable with the two other methods.

Therefore, the permuted block by block method has strong relative efficiency in comparison with the PB method and the permuted block method employing different sized blocks under the corresponding conditions.

Motivating Data

A randomized, double-blind, placebo-controlled study was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic of linagriptin (low dose, middle dose, and high dose) administered orally once daily for 28 days in Japanese patients with type 2 diabetes mellitus comparing with placebo [13]. The pair wise comparison of each dose group with the placebo group was made from the high dose sequentially by using the closed testing procedure [14]. The matrix for randomization was generated by the permuted block by block randomization described in Generation of matrix.

Table 5: Number of randomized patients into each treatment in each center( ): RI.

	L	M	H	P	Total
Center 1	6	6	6	7	25
Center 2	3	3	3	3	12
Center 3	5	5	4	5	19
Center 4	3	3	2	1	9
Center 5	1	1	2	2	6
Total	18	18	17	18	71 (0.94)

In total, 71 patients with type 2 diabetes mellitus were randomized into four groups at five centers by using the matrix. However, the assigned block numbers of were various in each center (from two to nine). It was determined by the possibility of enrollments in each center, which was surveyed by the investigator at each center before the start of study. Patients were equally randomized into all dose groups (low dose: 18 patients, middle dose: 18 patients, high dose: 17 patients, and placebo: 18 patients) in this study. RI was 0.94. Table 5 shows the number of randomized patients in each group in each center. The largest difference in the number of randomized patients among centers was two (Center 4). The number of randomized patients into each treatment group had imbalances but was acceptable. The permuted block by block randomization worked well in the actual clinical trial where investigators did not randomize patients into the complete number of block size.

Discussion

When patients are completely randomized into the block size in each center, over 11 blocks let the RI be 0.90 in the permuted block by block randomization. Even if the total number of randomized patients is 15, the RI shows as 0.75.

RI is always 1.00 in the permuted randomization proposed by Zelen when investigators randomize patients into the complete number of block size.

RI was defined by the ratio of the largest number of randomized patients into a group to the smallest number of randomized patients

into a group. It completely influences on study power. In case that the same number of patients is randomized and made pair wise comparison, study power is the highest.

Incomplete randomization of patients into the block size in each center induces an imbalance in the randomization. This situation always happens in a clinical study. However, it is difficult to make assumptions about the number of centers where patients are incompletely randomized or the number of randomized patients in the incompletely randomized centers. There is sure to be some difference in the number of patients randomized in each center in clinical trials. Additionally, investigators cannot randomize the complete number of block size in their centers. We, therefore, simulated the limited cases in results to compare among three randomization methods. The RIs of permuted block by block randomization were preferable under the estimated conditions. The permuted block by block randomization can be applied to a clinical study because of its low predictability. In fact, we applied our proposed permuted block by block method to the actual clinical study illustrated in motivating data. One of the objectives of this study was to investigate the control of fasting plasma glucose by investigational drug in a dose response manner. We wanted to show the dose response relationship and find some effective dose to control the fasting plasma glucose of patients. The numbers of block allocations to centers were from two to nine. The actual total numbers of randomized patients were from six to 25 among centers. RI was 0.94 in spite of the incomplete randomization in almost all centers. The application of permuted block by block randomization was, therefore, assumed to apply to a study where several dose groups are set.

The strongest methods to avoid bias in a clinical study are randomization and blinding. Applying randomization and blinding can exclude various biases from the results of clinical studies, and results without bias have high generalizability. Randomization reduces the selection bias that enable investigators to freely know the randomization order and obtain excellent results by allocating investigational drugs to mild patients and controls to severe patients [15]. Randomization reduces that bias to lower the predictability of the drug to be treated. The effect of the drug is then fairly assessed in the randomized clinical study.

Therefore, Status categorized the results of randomized clinical trials as the strongest evidence in evidence based medicine [16]. However, even if randomization is applied to a clinical study, not all biases can be avoided. Application of randomization and blinding to a clinical study does make strong evidence. We have some studies that blinding cannot be applied because of ethics or logistics in some clinical studies, and predictability increases when PB randomization is applied to those studies.

The permuted block method employing different sized blocks as proposed by Schulz [17] is effective in reducing predictability by adjusting the possible randomized patients in each center. However, it is not necessarily an appropriate method for a dose response study which includes several dose groups since the number of all treatment groups is large. If patients are completely randomized into the block, the imbalance is prevented because a block includes all treatment groups at least once. Unfortunately it is impossible in a clinical study. The probability of imbalance among treatment groups increases if the block size is large because the permuted randomization balances the patient number by completing the block. RIs decrease as the incomplete randomization increases (Table 4). Furthermore, the permuted randomization employing the different block size is not effective for avoiding selection bias when the study is open labeled.

Our proposed method can improve the predictability of PB randomization. Even if the block size is known in an open labeled study, the permuted block by block method makes it impossible to predict the treatment group situated at each code by attaching the code which shows “change to control” or “no change”. Investigators immediately have known whether they administered active or placebo medication to a patient when they randomize patients and open this attached code.

The ideal permuted randomization is a small and unpredictable block size for the subsequent randomized treatments. The block is basically assigned to a center because most investigators want to assess all treatment groups. It means investigators in each center randomize patients to fulfill the block size. If doing so, almost the same number of patients is randomized in each treatment group in each center. Incomplete randomization rarely happens in centers when the bock size is small. The probability of predicting the subsequent randomized treatment is higher because the block size is small [8]. However, the block size is smaller but predictability is lower in our proposed method, which has the two distinguished properties of less predictability and small block size.

The imbalance of randomization is permitted under certain conditions even if patients are randomized into the whole matrix in the permuted block by block method because the “no change” block, which includes only active treatments, is regularly set in the matrix. This causes an imbalance in the randomized number into each treatment group and reduces the power of the study. However, imbalances in the range of 0.75 to 1.00 have a small effect on relative efficiency for sample mean [10]. The comparison of binary variables, for example healing rates, would be similar. Therefore, the imbalance of the permuted block by block method is acceptable.

In conclusion, our proposed permuted block by block randomization works well in clinical studies, especially in a dose response study.

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