Application of Cluster-Randomized Controlled Trial in Health Management of Hepatitis B

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Abstract: Objective: To explore the feasibility of cluster-randomized controlled trial in the health management of hepatitis B. Methods: The samples of intervention group and control group were determined according to the method and principle of cluster-randomized controlled trial. To investigate the applicability of cluster randomization in the intervention of hepatitis B health management, the intervention measures of health propaganda in the health management of hepatitis B patients were whether they could take medicine regularly according to doctor's advice. Results: The significance of the two groups was judged by general test, and then the statistical significance between the two groups was judged by adjusting the test. Conclusion It is proved that cluster-randomized controlled trial is feasible in the health management of hepatitis B. It should be noted that the effect of variance expansion on the results should be adjusted in statistical analysis.

Keywords: Cluster-randomized controlled trial; Hepatitis B; Hearth management

1. Introduction

Nowadays, Hepatitis B virus (HBV) infection is a serious public health problem in China. It can cause harm to people's health and economic development. Currently, the primary treatment for hepatitis B is antiviral therapy. However, due to the lack of systematic understanding of the disease and the perfect drug supervision, most patients are unable to adhere to the doctor's advice for a long time, affecting the treatment effect [1]. It is imperative to establish an effective management model to control the infection of HBV and decrease the morbidity of hepatitis B in China. Health management prevents and controls various health risk factors of individuals and people in a comprehensive monitoring, analysis, assessment, and prediction manner [2]. It can effectively use limited health resources to meet health needs to achieve the best results. At the same time, there are a large number of infected people in China's hepatitis B, with high morbidity, poor prognosis and a great negative impact on society. However, it is difficult to conduct non-random sampling in individual studies in these populations. However, it is difficult to do non-random sampling in individual studies among these populations. This is because the characteristics of hepatitis B make it easy for researchers to introduce confounding factors into the determination of research samples and bring bias to research and analysis. Cluster-randomized controlled trial is a randomized epidemiological method based on population, which is often used in intervention research. It has been well applied in related research. This paper is based on the principle and method of cluster-randomized controlled trial, through the design of intervention cluster-randomized controlled trial in hepatitis B health management intervention.

2. Method

In the experiment design, the research object is group, and the statistical analysis is individual. The unit of randomization is population, while the unit of statistical analysis is each infected person. Unit inconsistency of randomization and statistical analysis is the essential difference between group random test and individual random test. The main difference between group random test and cluster random sampling survey is that cluster random sampling randomly extracts a certain number of groups from a given population, but it does not involve randomly assigning these groups to different groups for intervention trials, and in each group random test. Within the cluster, the selection of individual samples can be carried out by random sampling or non-random sampling according to the need [3-5]. In the experiment, the subjects were selected by the treatment group. Individuals in the same group have some similarities because of some common factors or the interaction between them, which leads to a certain correlation in the group. Using traditional statistical analysis methods directly may lead to wrong conclusions.

The mathematical derivation of intra-group correlation coefficients is as follows:

$$\sigma^2 = \sigma_a^2 + \sigma_w^2 \quad \text{so:} \quad \rho = \sigma_a^2 / \sigma^2 = \sigma_a^2 / \left(\sigma_a^2 + \sigma_w^2\right) \tag{1}$$

The intra-group correlation is expressed by the intra-group correlation coefficient ρ. If the total variance is σ^2, the inter-group variance is σ_a^2, Sample estimates can be obtained by using the principle of variance:

$$r = s_a^2 / (s_a^2 + s_c^2) = \frac{(MS_c - MS_w)}{[MS_c + (m_0 - 1)MS_w]} \quad (2)$$

In the formula, MS_a and MS_c are inter-group mean square and intra-group mean square in variance analysis, and M_0 is the corrected observation unit.

Sample estimates for sum, respectively. In the binomial classification variables of the two groups, it is assumed that k_i groups are randomly assigned to the I intervention group, $i = 1,2\ldots$; p_{ij} represents the sample rate of group J of group i, pi represents the sample rate of group i; m_{ij} represents the observation number of group J of group i, M_i is the observation number of group i, m and K are the total number of observation objects and the total number of groups extracted [6-11].

$$MS_w = \frac{\sum_{i=1}^{2}\sum_{j=1}^{k_i} m_{ij} p_{ij}(1 - p_{ij})^2}{(m - k)} \quad (3)$$

$$MS_c = \frac{\sum_{i=1}^{2}\sum_{j=1}^{k_i} m_{ij}(p_{ij} - p_i)^2}{(k - 2)} \quad (4)$$

Similarly, the MS_c and MS_w formulas for the comparison of the two groups are as follows:

$$MS_c = \frac{\sum_{i=1}^{2}\sum_{j=1}^{k_i} m_{ij}(X_{ij} - X_i)^2}{(k - 2)} \quad (5)$$

$$MS_w = \frac{\sum_{i=1}^{2}\sum_{j=1}^{k_i}\sum_{l=1}^{m_{ij}} (X_{ijl} - X_i)^2}{(m - k)} \quad (6)$$

$$m_0 = \frac{m - \sum_{i=1}^{2} \overline{m}Ai}{(k - 2)} \quad (7)$$

$$\overline{m}Ai = \frac{\sum_{i=1}^{k_i} m_{ij}^{\ 2}}{m_i} \quad (8)$$

X_{ijl} in the formula represents the lth observation value in group J of group I. X_{ij} is the mean of group J of group I and X_i is the mean of group I.

The variance of sample mean of cluster random sampling is as follows:

$$\sigma_x^2 = \frac{\sigma^2}{km}[1 + (m - 1)\rho] \quad (9)$$

In addition to the intra-group correlation coefficients, the influence of variance inflation factor (IF) on sample size estimation should be taken into account when analyzing the results of cluster randomized trials. In statistical analysis, group randomized trials need special methods. Donner and Donald put forward a test formula for adjusting group effects [12]:

$$X_A^2 = \sum_{i=1}^{2} \frac{m_i(p_i - p)^2}{C_i p(1 - p)} \quad (10)$$

In the formula, MI is the observation unit of group I, PI is the sample rate of group I, P is the total rate of two groups, C_i is the variance expansion factor of group I, and the formula is:

$$C_i = 1 + (\overline{m}Ai - 1)r \quad i = 1,2 \quad (11)$$

A randomized trial involving two treatment groups was hypothesized. There were m groups in each group and n individuals in each group. For the mean comparison, the number of individuals required for each treatment group was as follows:

$$n = \frac{(Z_{1-\partial/2} + Z_{1-\beta})^2 \cdot 2\sigma^2[1 + (m - 1) \cdot \rho]}{(p_1 - p_0)} \quad (12)$$

In the two-rate comparison, the number required for each group is:

$$n = \frac{(Z_{1-\partial/2} + Z_{1-\beta})^2 [p_1 \cdot (1 - p_1) + p_0 \cdot (1 - p_0)]}{(p_1 - p_0)^2} \quad (13)$$

The number of groups of two groups: $k = m / n$, α is the error probability of type I, β is the error probability of type II, σ is the standard deviation, and ρ is the correlation number within the group.

3. Application Design

To observe the effect of two-year health lectures on the medication status of hepatitis B patients according to doctor's advice, a cluster random design and sample size estimation were conducted in the city as a unit. Assuming that the probability of allowable type I errors is 0.05, the test efficiency is 0.8, the non-compliance rate of hepatitis B patients in the intervention group after two years of intervention is 0.15, the control group is 0.25, and the intra-group correlation coefficient is 0.04. According to the above formula, it can be concluded that the intervention group and the control group need about 1230 hepatitis B patients respectively. If 205 people were investigated in each city, the two treatment groups need 6 cities respectively. Without considering the variance expansion of group effect, i.e. p=0, the sample size required for two groups is 137 according to the above formula, which greatly underestimates the sample size required for group random experiments. The 12 cities were divided into two groups, intervention group and control group. In the intervention group, the contents of health education related to hepatitis B, and popularization of medication intervention [13]. No measures were taken in the control group. Two years later, 1230 hepatitis B patients were selected from both groups to investigate the situation of taking medicine according to doctor's advice in the last half year, and calculate the rate of taking

medicine not according to doctor's advice in the last half year. To analyze the difference between the intervention group and the control group of hepatitis B patients who did not take the medicine according to the doctor's advice in the last six months. Data is shown in Table 1.

Table 1. Ratio of patients with hepatitis B who did not take medicine according to doctor's advice

Number	Intervention city	Number	Control city
1	A1/205	1	B1/205
2	A2/205	2	B2/205
3	A3/205	3	B3/205
4	A4/205	4	B4/205
5	A5/205	5	B5/205
6	A6/205	6	B6/205
Total: $\sum_{i=1}^{6} A_i / 1230 = C, \sum_{i=1}^{6} B_i / 1230 = D$			
Total: $(\sum_{i=1}^{6} A_i / 1230 + \sum_{i=1}^{6} B_i / 1230) / (1230 + 1230) = E$			

The significance of the two groups was judged by common test, and then the statistical significance between the two groups was judged by adjusting the test. Finally, we observed whether the general test results were the same as the adjusted test results. The results are the same, which shows that the test method of group random experiment is the same as that of general random test, but the results are different because the variance expansion occurs in group random experiment. In this case, the use of ordinary testing will produce greater bias, and the adjusted test formula should be adopted.

4. Discussion

Cluster-randomized controlled trials can reduce the problems caused by non-random sampling. Compared with individual trials, Cluster-randomized controlled trials have the following characteristics: cluster-randomized design is a research method based on the observation unit of the group, and there is no need for randomized selection of individuals in the study [14]. This method is very conducive to the study of interventions for infectious diseases. because there is certain intra-group correlation among individuals in a random sample. The decrease of statistical efficiency of Cluster-randomized controlled trials is related to the intra-group correlation coefficient. Because the group random experiment is based on the group, each group is composed of different individuals. Therefore, it is difficult to ensure that the baseline information of the intervention group is consistent with that of the control group. Especially in the case of fewer research groups, it is easy to produce confusion. Cluster-randomized controlled trials are often open and difficult to achieve double blindness. It is necessary to obtain the informed consent of the subjects in the study. This will lead researchers and subjects to understand the intervention measures beforehand, so it is also prone to selective bias [15].

We should pay attention to the following problems when carrying out Cluster-randomized controlled trials in the health management of hepatitis B: The calculation of sample size of group randomized design is not exactly the same as that of individual randomized design, and we should consider not only the selection of equivalence test, superiority test and non-inferiority test methods [16]. The selection of critical value and unilateral and bilateral tests should also be considered. The small sample size may make the research ineffective. No difference can be found. The analysis of the test results can be divided into two categories: individual analysis and group analysis. Inter-group effects should be considered in individual analysis. Ignoring the correlation of data will increase the probability of category I errors.

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