FABAD J. Pharm. Sci., 28, 113-122, 2003

SCIENTIFIC REVIEW

Reducing the Bias in Clinical Trials (Randomization & Blinding)

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Reducing the Bias in Clinical Trials (Randomization and Blinding)

Summary : *The term bias in clinical trials describes the systematic influence of any factors associated with the design, conduct, analysis, and interpretation of the results. The two common methods that are used to reduce the bias are randomization and blinding. Randomization aims to obviate the systematic differences (or bias) between groups due to the factors other than the treatment. Randomization gives each patient a known (usually equal) chance of being assigned to any of the groups and it is based on the premise that the group assignment cannot be predicted. Blinding (or masking) is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients, the responses of subjects to the treatments, the evaluation of responses, the handling of withdrawals, the exclusion of data from analysis, and so on. There are different randomization and blinding methods. In this review, the randomization and blinding methods used to reduce bias will be discussed with appropriate examples.*

Key Words: *Clinical trials, Bias, Randomization, Blinding.*

Klinik Deneylerde Yanlılığın Azaltılması (Rasgelelik ve Körleme)

Özet: *Klinik deneylerde yanlılık; deneyin tasarlanması, yönetilmesi, sonuçların analizi ve değerlendirilmesinde herhangi bir faktörün sistematik etkisi olarak tanımlanmaktadır. Yanlılığın azaltılmasında yaygın olarak kullanılan yöntemlerden ikisi rasgelelik ve körlemedir. Rasgelelikteki amaç; gruplar arasında, incelenen tedavi yöntemi dışındaki faktörlerden kaynaklanan sistematik farklılıkları (ya da yanlılığı) önlemektir. Rasgelelilikte, tedavi grupları hastalara bilinen bir olasılıkla (genelde eşit bir olasılıkla) atanır ve rasgelelik bu grup atamalarının önceden kestirilemez olması temeline dayanır. Körleme (ya da maskeleme), uygulanan tedavinin bilinmesi nedeniyle, hastaların deneye seçilmesi ve deney gruplarına atanmasında, hastaların tedavilere verdikleri yanıtlarda, bu yanıtların değerlendirilmesinde, deneyden ayrılmaların ele alınma aşamasında, analizlerden veri çıkartmada vb. ortaya çıkabilecek bilinçli veya bilinçsiz yanlılıkları azaltmayı amaçlamaktadır. Birçok farklı rasgeleleme ve körleme yöntemi bulunmaktadır. Bu derlemede, yanlılığı azaltmakta kullanılan rasgelelik ve körleme yöntemleri üzerinde örneklerle durulacaktır.*

Anahtar kelimeler: *Klinik deneyler, Yanlılık, Rasgelelik, Körleme*

INTRODUCTION

A clinical trial is a planned experiment on human subjects that is designed to evaluate the effectiveness of one or more treatments. Recently invented drugs, surgical methods, psychological treatment methods, dietary methods, etc. may be included as the treatments in a trial. Some important questions, such as the side effects and complications of the applied drug or treatment, in which circumstances, in what doses and for how long the drug or treatment may be applied, may be answered by the clinical trials. On the other hand, no individual clinical trial can be expected to be totally representative of future patients because of possible influences of geographical location, the time when it is conducted, the medical practices of particular investigators and clinics, and so on[1-5].

Clinical trials are performed at least in two groups, one being the control group, in order to compare the results of the patients who receive a new treatment (or a new drug) to those patients with similar characteristics (control group) who receive another treatment (or another drug). The treatment method or drug that is to be applied to the control group is generally a standard treatment method or drug with proven effectiveness. However, the other treatment

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method mentioned here is not necessarily an active treatment method. If there is no ethical problem, no active treatment method or drug may be applied to the control groups -- in other words, a dummy treatment procedure (also called placebo) may be applied to the control group.

BIAS

The crucial point of a clinical trial is the aim of investigating the difference of the patient groups caused only by the treatment procedures that are applied. If other kinds of differences exist (such as systematic differences) between the groups to be formed, then the outcomes are supposed to be biased. The term bias describes the systematic tendency of any factors associated with the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value[1]. In other words, the possible reasons for the differences between the groups at the end of the study will be factors other than the applied treatment procedures when the trial is biased, and the conclusions shall not be valid due to such bias. Thus, determining the potential sources of bias as much as possible is very important in order to reduce such bias in the trial[1, 3, 6, 7].

One of the possible sources of bias may occur in the design phase of the trial. For example, assignment of the patients at lower risk to one group and the patients at higher risk to the other group may be cause of bias and the interpretations at the end of the study will probably be inappropriate as a result[1, 2]. Other sources of bias may occur during the conduct and analysis of a clinical trial. For example, protocol violations and exclusion of patients from analysis based upon knowledge of subject outcomes are possible sources of bias that may affect the accurate assessment of the treatment[1].

The most common design techniques for avoiding bias in clinical trials are **randomization** and **blinding.**

RANDOMIZATION

Randomization aims to obviate the systematic differences (or bias) between groups due to the factors other than the intervention. It gives each patient a known (usually equal) chance of being assigned to any of the groups and it is based on the premise that the group assignment cannot be predicted[2,3,4,7]. It also tends to provide treatment groups with similar distributions of prognostic factors (known and unknown)[1,7,8,9]. For this reason, randomization must be distinguished from haphazardness[3, 6].

The most common randomization methods are **simple, weighted, block and stratified randomization**[2,3,4,7,10].

1. Simple Randomization

The simplest method of randomization is tossing a coin or rolling a fair die. For example, heads (H) and tails (T) of a coin may represent treatments A and B, respectively. An allocation scheme for the patients who will participate in the trial may be formed by tossing a coin in the design phase of the experiment (Table 1). Similarly, the odd and even numbers of a fair die may represent treatment A and treatment B, respectively.

Table 1. An allocation scheme for the patients by tossing a coin

No. of the Patient	1	2	3	4	5	6	.	.	n
Outcome	H	H	T	H	T	T	.	.	T
Treatment method	A	A	B	A	B	B	.	.	B

However, the assignment process is generally carried out using a table of random numbers or a random number generator on a computer. Table of random numbers may be found in most of the basic statistics – biostatistics text books and these tables may differ[3,4,6,7,11]. An example of table of random numbers with 40 blocks and 25 rows is given in Appendix A[12]. As each number in these tables occurs equally often,

they are totally unpredictable. On the other hand, there are modules that generate random numbers in the statistical software packages. For example, in the SPSS, a uniform distribution between the required numbers may be generated by the directory *Transform / compute / RV.UNIFORM (min, max).*

If there are two treatment procedures that we want to investigate, we may choose odd numbers to represent one of the treatments (group) and even numbers to represent the other treatment (group). In such an assignment, the very first step is to determine the corresponding numbers to the treatment procedures. Then, a column between 1 – 40 is selected (it may be selected from any of the columns or rows depending on the researchers' desire). The 15 two-digit numbers selected from the columns 13 and 14 in the Appendix A are given in Table 2:

Table 2. The selected two digit numbers from columns 13 and 14 in App. A

83	53	40	05	75	33	01	26	42	94	62	86	17	77	79

If we select odd numbers to represent Treatment A and even numbers to represent Treatment B, the appropriate assignment scheme of the 15 patients shall be as shown in Table 3.

Table 3. The assignment scheme of two treatments by random numbers in Table 2

No of Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Treatment Procedure	A	A	B	A	A	A	A	B	B	B	B	B	A	A	A

According to this assignment scheme, if no patient is accepted to the trial after the 15th patient, there shall be nine patients in group A and six patients in group B. If it is strictly desired to have equal number of patients in each group, then treatment B shall be assigned to the next three patients in order to equalize the number of the patients in each group.

On the other hand, some problems may occur in simple randomization for the assignments made by either tossing a coin or using a table of random numbers. For example, assume that in an assignment process performed for 20 patients, treatment A is assigned to the first 10 patients and treatment B is assigned to the other patients. In such a case, if the outcome variable is affected from a seasonal difference, then the outcomes would probably be biased.

A similar assignment can be performed by taking only one column into consideration. If we only consider the 13th column for the first 15 patients in the above example, the assignment will be as shown in Table 4 (zeros "0" will be ignored):

Table 4. The assignment scheme of two treatments according to 13th column of table of random numbers (App. A)

No of Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Treatment Procedure	B	A	B	A	A	B	B	A	B	B	A	A	A	A	B

Another approach to the same question may be the selection of the numbers between 00–49 for treatment A and 50– 99 for treatment B. Thus, there are numerous ways of assignment by using the table of random numbers and any method may be used.

This latter method of assignment may be easily applied in the trials with more than two treatments (groups). For example, in a trial where three different treatments such as A, B and C shall be assigned, the plan below may be applied:

Between 01 – 33	Treatment A
Between 34 – 66	Treatment B
Between 67 - 99	Treatment C

According to this assignment plan, the assignment of 15 patients in our above examples is shown in Table 5.

Table 5. Assignment of 15 Patients For A Three Treatment Trial

No of Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Treatment Procedure	C	B	B	A	C	A	A	A	B	C	B	C	A	C	C

2. Weighted Randomization

Assignments may be weighted by making small changes in simple randomization procedures. For example, if the number of patients that shall be assigned to treatment A is desired to be double the number of patients assigned to treatment B, then choosing the numbers between 01 – 66 for treatment A and numbers between 67 – 99 for treatment B from the table of random numbers would be sufficient[3].

3. Block Randomization

As may be easily concluded from the explanations and examples of simple randomization, in such ways of randomization the number of the patients assigned to groups generally differs. On the other hand, in most of the studies the number of the patients is desired to be very close or equal in the different groups. With the help of block randomization, the number of patients in different groups is balanced as much as possible[2,3,4,7,13].

In block randomization, the blocks may be in any size. However, a multiple of the number of treatments is usually preferred for the block size. For example, if there are two treatment procedures, then it is better to use blocks of size 2, 4, 6 … and if there are three treatment procedures, blocks of size 3, 6, 9 … are preferred.

3.1. Two-Sized Block Randomization for Two Treatments

There are two possible block types when there are two treatment procedures and when the block size is supposed to be 2:

1. AB	2. BA

When we use the 14th column of the table of random numbers (Appendix A) and ignore the numbers different from 1 and 2 then we have the below sequence for the blocks:

1	2	2	2	2

When we make the block assignment according to this sequence, the assignment of the treatments will be as shown in Table 6. As can be seen, there will be five patients in both treatments A and B in the final assignment.

Table 6. Allocation scheme in two-sized block randomization

Block	1		2		2		2		2	
No of Patient	1	2	3	4	5	6	7	8	9	10
Treatment Procedure	A	B	B	A	B	A	B	A	B	A

3.2. Four-sized Block Randomization for Two Treatments

When we consider blocks of size four for two treatment procedures, then there will be six different combinations in which two patients would be assigned to treatment A and two to treatment B,

1. AABB	2. BBAA	3. ABAB	4. BABA	5. ABBA	6. BAAB

If we use only these six different combinations in the assignment process of the treatments, then the number of the patients in one group may differ at most by two patients from the other group at any given time; however, the difference would not usually be more than one. When we select the 13th column of the table of random numbers and ignore the numbers different from 1 – 6, we get the below sequence,

5 4 3 2 4 6 1 3 2 3

The assignments of the patients when the first four numbers of this sequence are used is shown in Table 7:

Table 7. Allocation in four-sized blocks

Block	5				4				3				2			
No of Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Treatment	A	B	B	A	B	A	B	A	A	B	A	B	B	B	A	A

Block sizes are not restricted. For example, for a block of six, possible combinations would be in the form of AAABBB, ABABAB, ABAABB, … . However, large blocks should not be used since such design would make the groups more unbalanced.

3.3. Six-sized Block Randomization for Three Treatments

The large sized blocks are not preferred in the studies where block design is used. For example, when there are three different treatment procedures and the block size is considered to be six, then we get different block structures (Table 8), and this may cause trouble for the researcher.

For example, assume that 30 patients will be assigned in this trial. As each block consists of six patients, it is enough to select five blocks. When we select the first two columns of the table of random numbers, the sequence will be as follows;

23, 05, 14, 38, 97, 11.

In this sequence, we ignore 97 as we have 90 blocks. Thus, five blocks (blocks 23, 05, 14, 38 and 11) consisting of 30 patients have the assignments below:

1. ACCBAB 2. AACBBC 3. CCBBAA 4. ABCBAC 5. BBCAAC

By this sequence, the 1st patient will be assigned to treatment A, the 2nd to treatment C, the 14th to treatment C and the 30th to treatment C. At the end of the research there will be 10 patients in each group.

In clinical trials it is generally desired to keep the randomization sequence hidden from the people who actually determine the treatment procedures. For this reason, sometimes two-sized, four-sized and six-sized blocks may be needed to be used together.

4. Stratified Randomization

While simple randomization methods eliminate the bias caused by allocation procedures, it does not strictly guarantee an unbiased structure. For example, it does not guarantee that the patients in each group show similar age characteristics. Especially in small studies, it is more likely that some differences

Table 8. 90 Block combinations for three different treatment procedures

1. AABCBC	11. BBCAAC	21. ABBCCA	31. CAACBB	41. ABCCAB	51. BCABCA	61. CABABC	71. CBACAB	81. BABCCA
2. AABBCC	12. BBACCA	22. ACCABB	32. CAABCB	42. ABCCBA	52. BCAACB	62. CABBAC	72. CBACBA	82. BCBCAA
3. AACCBB	13. CCBABA	23. ACCBAB	33. CAABBC	43. BACABC	53. BCACAB	63. CABBCA	73. ABABCC	83. BCBACA
4. AACBCB	14. CCBBAA	24. ACCBBA	34. CBBCAA	44. BACBAC	54. BCACBA	64. CABACB	74. ABACBC	84. BCBCCA
5. AACBBC	15. CCAABB	25. BAABCC	35. CBBACA	45. BACBCA	55. ACBABC	65. CABCAB	75. ABACCB	85. CACABB
6. AABCCB	16. CCABAB	26. BAACBC	36. CBBAAC	46. BACACB	56. ACBBAC	66. CABCBA	76. ACACBB	86. CACBAB
7. BBACAC	17. CCABBA	27. BAACCB	37. ABCABC	47. BACCAB	57. ACBBCA	67. CBAABC	77. ACABCB	87. CACBBA
8. BBAACC	18. CCBAAB	28. BCCBAA	38. ABCBAC	48. BACCBA	58. ACBACB	68. CBABAC	78. ACABBC	88. CBCBAA
9. BBCCAA	19. ABBACC	29. BCCABA	39. ABCBCA	49. BCAABC	59. ACBCAB	69. CBABCA	79. BABACC	89. CBCABA
10. BBCACA	20. ABBCAC	30. BCCAAB	40. ABCACB	50. BCABAC	60. ACBCBA	70. CBAACB	80. BABCAC	90. CBCAAB

will occur between groups due to the chance factor and this may cause trouble in interpreting the results. Even in the studies with more than 100 patients, there may be some significant variations especially for rare characteristics[3,4,7,11,13].

In many clinical trials, it is pre-known that sub-groups of patients respond differently to the treatment. For this reason, the patients in each group should have similar characteristics in such cases.

With the help of stratified randomization, patients' characteristics that are important and prognostic can be balanced without sacrificing the advantages of randomization. Briefly, the aim of stratified randomization is to make the chosen prognostic characteristics or other patient factors as similar as possible for each treatment group. Stratified randomization may also prevent the imbalances that may occur by chance. In stratified randomization, block randomization is used for each strata. Simple randomization should not be preferred because of the possible imbalances among strata.

The first step in stratified randomization is to form block sets for all combinations of prognostic factors. For example, if it is necessary to balance the groups according to gender, then two block sets are formed for each gender (Table 9).

Table 9. Stratified randomization for two treatment groups (Block size = 4)

Male	ABAB	AABB	BBAA	AABB	…
Female	BAAB	BABA	ABAB	BBAA	…

According to this assignment sequence, the male patients will be assigned to treatment A, B, A, … and female patients will be assigned to treatment B, A, A, …, respectively. If the study is stopped at the fourth block, then eight females and males will be assigned to treatments A and B. Thus, the groups will be balanced according to gender.

Similarly, in a trial for breast cancer with two different drugs, one of the suitable stratification factors may be the menopausal status of the patient. A similar plan for pre- and post- menopausal women may be prepared as above.

Stratified randomization may also be used for two or more stratification variables. Assume that the tumor size is an additional stratification variable for the above breast cancer example. If we categorize the tumor size in two groups such as £ 4 and > 4, we get a 4-strata (2 for menopausal status, 2 for tumor size; 2x2=4) study. An example for this allocation is given in Table 10. Here, block randomization is applied for each stratification factor. As opposed to block randomization, it is necessary to form a different block sequence for all stratification factors in stratified randomization. When we choose the first four columns of the table of random numbers for the stratification factors in our example and ignore the numbers not in the range 1 – 6 we get the sequences: (2, 1, 3, 1) for the first stratification factor, (3, 5, 4, 1) for the second, (1, 5, 3, 3) for the third and (5, 4, 1, 4) for the last. These number sequences represent the six blocks given in the example of block randomization and generate the assignment sequence shown in Table 10:

Table 10. Stratified randomization for two factors

Menopausal Status	Tumor Size	BLOCKS					
Pre-menopausal	≤ 4	ABAB	AABB	ABBA	AABB	…	…
	> 4	ABBA	BABA	BBAA	AABB	…	…
Postmenopausal	≤ 4	AABB	BABA	ABBA	ABBA	…	…
	> 4	BABA	BBAA	AABB	BBAA	…	…

In other words, the first pre-menopausal patient with tumor size ≤ 4 will be assigned to treatment A and the first post-menopausal patient with tumor size >4 will be assigned to treatment B.

We may add the node involvement as a third stratification variable to our example. If we categorize node involvement in three groups such as 0, 1 – 4 and

5+, we get a 12-strata (2x2x3=12) study. However, to study with more strata may result in imbalanced assignment of treatments to the groups. For this reason, especially in small studies, it is not practical to use more than two stratification factors. When it is really essential to stratify for more than two groups, minimization can be used.

Minimization

The only acceptable non-randomized allocation method alternative to randomization is minimization. Minimization is an effective method that ensures a perfect balance between groups for many prognostic factors even in small samples. It has some definite advantages over simple and stratified randomization when the sample size is small[3].

Minimization is based on a completely different principle from randomization. For example, if the order of being accepted to the trial is taken into consideration in a clinical trial, the first patient is allocated randomly. Afterwards, the treatment that provides a better balance between the groups is evaluated according to the concerned prognostic characteristics for each subsequent patient1. The patient is then allocated to a treatment group according to whichever minimizes the imbalance between the groups with a probability greater than 0.5. The probability is generally taken to be 1 to make the design more balanced and easy to handle.

For example, suppose we extend the example given in stratified randomization and add another stratification factor such as node involvement (0, 1 – 4 or 5+). In such trials with more than two stratification factors (or prognostic characteristics), especially when a small-scaled study is planned, it is not practical to apply stratified randomization since it would be much harder to achieve a good balance between the groups. Especially when one of the stratification factors is very rare, it is inevitable that there will be some imbalances between the groups. For these reasons, the best method to be used in such trials is minimization. Now assuming that there are two groups (control and treatment) in this trial and that the trial is supposed to cover 30 patients, our stratification factors will be as shown in Table 11:

Table 11. The stratification factors for breast cancer example

Menopausal Status	Tumor Size	Node Involvement
Pre-menopausal	≤4	0 1 – 4 5+
	≥5	0 1 – 4 5+
Post-menopausal	≤4	0 1 – 4 5+
	≥5	0 1 – 4 5+

The sub-totals of each factor are as shown in Table 12 after 29 patients are accepted for this trial.

Table 12. The distribution of the first 29 patients by their characteristics in a clinical trial using minimization approach

Factors	Factor Levels	Treatment Group (Total # of patients =15)	Control Group (Total # of patients =14)
Menopausal Status	Pre Post	7 8	7 7
Tumor Size	≤4 ≥5	9 6	8 6
Node Involvement	0 1 – 4 5+	1 9 5	1 8 5

Assume that the next patient (30th patient) is postmenopausal with tumor size 3 and node involvement 5. The imbalance totals for women with same characteristics are shown in Table 13. Since our aim is to balance the groups to the extent possible, the most suitable treatment for the next patient is the group with the smallest total. Thus, as the totals (to-

tal of highlighted characteristics) in our groups are 22 and 20 for experiment and control groups, respectively, we assign this patient to the control group to provide a better balance.

Table 13. Calculation of imbalance in patient characteristics for allocating the treatment to the 30th patient

Factors	Factor Levels	Treatment Group (Total # of patients =15)	Control Group (Total # of patients =14)
Menopausal Status	Post	8	7
Tumor Size	≤4	9	8
Node Involvement	5+	5	5
Imbalance Totals	22	20	

After a patient is allocated to a treatment, the totals in the table are updated and the process is repeated for the next patient. In case of equality of totals between groups the patient is allocated randomly (by simple randomization) as is the case for the first patient.

Blinding

Blinding (or masking) is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence that the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the responses of subjects to the treatments, the evaluation of responses, the handling of withdrawals, the exclusion of data from analysis, and so on[1]. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed[1,3,6,7].

As mentioned before, there are various possible sources of bias that may influence the results of the study in a clinical trial. One of these sources is possible preconceived notions of the patient receiving the treatment or of the assessor of the response to the treatment about the superiority of one treatment over another. If one of the patients or the assessors knows the treatment applied to the patient, this might influence the evaluation of response and lead to a biased result. Although such a biased assessment is generally made unconsciously and unintentionally, it may also be made intentionally. Such biased assessments are more likely to occur when the response to the treatment is subjective rather than objective[6].

One way of avoiding these biased assessments is to design the trial in such a manner that neither the patient nor any of the research staff in a clinical trial has any knowledge about the treatment given to the patient. Such trial designs are termed double-blind trials. In double-blind trials, the different treatments or drugs given to the patient must obviously be identical in shape and taste. The trial is said to be a single-blind trial if only the researcher or his/her staff knows which treatment is being applied to the patient, or very rarely vice versa. In an open-label trial the applied treatment is known by both patient and researcher.

It is desirable to use the maximum degree of blinding in clinical trials. This requires that the treatments to be applied during the trial should be completely indistinguishable by their characteristics (such as shapes, tastes etc. for drugs) either before or during administration, and that the blinding is maintained appropriately during the whole trial[1].

Some difficulties may arise in applying the double-blind procedure. For example, the treatments may have a completely different nature such as surgery and drug therapy. In such cases where a double-blind trial is not feasible, the single-blind method may be considered[1].

In single-blind trials, although it is easy to design the study and to make a decision about whether the patient should be excluded from the trial or not since the researcher knows the treatment being applied to the patient, there is a possibility of bias because of

the knowledge of the applied treatment. On the other hand, in some cases only an open-label trial is practically or ethically possible. Single-blind and open-label trials surely provide an additional flexibility, but in such trials the researcher or the patient himself may be a possible source of bias. It is thus very important that the researcher's knowledge of the next treatment should not affect his decision to enter the patient or his evaluation of the response of the patient.

For single-blind and open-label trials, central randomization by telephone, interactive voice response system, fax or Internet may be considered to avoid possible bias in accepting the patients to the trial. In addition, the clinical assessments should be made by medical staff who are not actually involved in treating the patients and who remain blind to treatment[1].

The blinding should be considered to be broken (for a single patient) only when knowledge of the applied treatment is deemed essential by the patient's physician for the patient's care[1].

Appendix A. TABLE OF RANDOM NUMBERS

	C O L U M N S									
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36	37-40
1	23 15	75 48	59 01	83 72	59 93	76 24	97 08	86 95	23 03	67 44
2	05 54	55 50	43 10	53 74	35 08	90 61	18 37	44 10	96 22	13 43
3	14 87	16 03	50 32	40 43	62 23	50 05	10 03	22 11	54 38	08 34
4	38 97	67 49	51 94	05 17	58 53	78 80	59 01	94 32	42 87	16 95
5	97 31	26 17	18 99	75 53	08 70	94 25	12 58	41 54	88 21	05 13
6	11 74	26 93	81 44	33 93	08 72	32 79	73 31	18 22	64 70	68 50
7	43 36	12 88	59 11	01 64	56 23	93 00	90 04	99 43	64 07	40 36
8	93 80	62 04	78 38	26 80	44 91	55 75	11 89	32 58	47 55	25 71
9	49 54	01 31	81 08	42 98	41 87	69 53	82 96	61 77	73 80	95 27
10	36 76	87 26	33 37	94 82	15 69	41 95	96 86	70 45	27 48	38 80
11	07 09	25 23	92 24	62 71	26 07	06 55	84 53	44 67	33 84	53 20
12	43 31	00 10	81 44	86 38	03 07	52 55	51 61	48 89	74 29	46 47
13	61 57	00 63	60 06	17 36	37 75	63 14	89 51	23 35	01 74	69 93
14	31 35	28 37	99 10	77 91	89 41	31 57	97 64	48 62	58 48	69 19
15	57 04	88 65	26 27	79 59	36 82	90 52	95 65	46 35	06 53	22 54
16	09 24	34 42	00 68	72 10	71 37	30 72	97 57	56 09	29 82	76 50
17	97 95	53 50	18 40	89 48	83 29	52 23	08 25	21 22	53 26	15 87
18	93 73	25 95	70 43	78 19	88 85	56 67	16 68	26 95	99 64	45 69
19	72 62	11 12	25 00	92 26	82 64	35 66	65 94	34 71	68 75	18 67
20	61 02	07 44	18 45	37 12	07 94	95 91	73 78	66 99	53 61	93 78
21	97 83	98 54	74 33	05 59	17 18	45 47	35 41	44 22	03 42	30 00
22	89 16	09 71	92 22	23 29	06 37	35 05	54 54	89 88	43 81	63 61
23	25 96	68 82	20 62	87 17	92 65	02 82	35 28	62 84	91 95	48 83
24	81 44	33 17	19 05	04 95	48 06	74 69	00 75	67 65	01 71	65 45
25	11 32	25 49	31 42	36 23	43 86	08 62	49 76	67 42	24 52	32 45

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