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Renal allograft immunosuppression

I. Early inflammatory and rejection episodes in triple drug treatment compared to double drug combinations or cyclosporin monotherapy

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Abstract. We have investigated the impact of triple drug immunosuppression on the occurrence of early inflammatory episodes, as detected by fine needle aspiration biopsy, and of episodes of clinical rejection during the immediate postoperative period. The prospective component of this study includes 128 consecutive first cadaveric renal transplant recipients receiving triple drug treatment consisting of azathioprine (Aza), cyclosporin (CyA) and methylprednisolone (MP). For controls we have used three historical groups: one immunosuppressed with Aza and MP (group A), another with CyA monotherapy (group B), and the third with CyA together with MP (group C) in equivalent drug dosages. On the average, 0.8 episodes of inflammation per patient were recorded during the immediate postoperative period of 30 days with triple drug treatment. This was significantly less than the 1.3 episodes in patients receiving Aza and MP ($P < 0.01$), the 1.7 episodes in patients on CyA monotherapy ($P < 0.001$), or the 1.6 episodes in patients receiving CyA together with MP ($P < 0.001$). Although the first episode of inflammation commenced concurrently in each group and the peak intensity of inflammation was the same, the mean duration of inflammation was significantly shorter – 2.7 days – under triple drug treatment than the 7.8–11.7 days for controls ($P < 0.001$). The frequency of rejection episodes under triple treatment was also significantly lower – 0.2 per patient – than the 0.8 per patient in controls ($P < 0.001$). The first rejection episode occurred later in the triple drug treatment group – on the average, on day 15.2 – than in the historical controls (on days 7.7–11.7). There was, however, no difference in the duration of rejection. There were no differences in patient survival between the four groups. Graft survival was 97% at 10 weeks for triple drug-treated recipients and 79%, 68%, and 87% for first grafts in groups A, B, and C, respectively. Disregarding a minor demographic bias for the triple drug-treated group with respect to preformed antibodies and preoperative dialysis treatment, the study suggests that the triple drug protocol, in the short run, is superior to any conceivable double drug combination or CyA monotherapy.

Key words: Kidney transplantation, triple drug therapy – Cyclosporin monotherapy, in kidney transplantation – Triple drug, double drug, and monodrug therapy, in kidney transplantation – Fine needle aspiration, in kidney transplantation

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Allograft rejection has been a major obstacle to successful transplantation. The majority of acute rejection episodes occur during the 1st weeks after cadaveric renal transplantation. High frequencies of acute rejections have been reported using conventional immunosuppression with azathioprine (Aza) and steroids [6, 10]. Various immunosuppressive protocols have been proposed, and they seem to have their virtues and vices. In addition to the conventional azathioprine and steroids [6, 9, 10], cyclosporin (CyA) alone [3] and CyA in combination with steroids, with or without prophylactic antithymocyte globulin [1, 8, 11], have been tried. Most centers, however, seem to turn to triple drug treatment, particularly for long-term immunosuppression [2, 4, 12].

In this study we have investigated the impact of triple drug immunosuppression on the occurrence of early inflammatory episodes, as detected by fine needle aspiration biopsy (FNAB), and episodes of clinical rejection during the immediate postoperative period. For controls we have used three historical groups: one immunosuppressed with Aza and methylprednisolone (MP), another with CyA monotherapy, and the third with CyA together with MP [7].

In subsequent studies, the experimental cohort of this study, immunosuppressed initially with Aza, CyA, and steroids, is randomized into four groups at 10 weeks post-transplantation and immunosuppression is continued with any combination of two drugs or with all three. A subsequent report will demonstrate whether it is safe to elimi-

nate one of the three drugs once the period of highest risk of rejection is over, and what the long-term consequences of the different double drug protocols are to the graft and to the recipient.

Patients and methods

Immunosuppression

Historical controls. Between 1981 and 1982 a total of 96 consecutive first and second cadaveric renal transplant recipients at the Fourth Department of Surgery, Helsinki University Central Hospital, were randomized to receive three different immunosuppressive regimens after transplantation. That in group A consisted of 2.1 mg/kg per day Aza ad infinitum (bone marrow and liver function permitting) plus high initial MP, beginning with 3.6 mg/kg per day and tapering down at 3-day intervals until the level of 0.5 mg/kg per day was obtained on day 15. Group B patients received 10 mg/kg per day CyA, adjusted to give a CyA plasma concentration of 100–300 ng/ml. In group C, CyA was administered as in group 2, together with high initial MP, beginning with 3.6 mg/kg per day and tapering down at 3-day intervals to zero on day 10. All acute rejection episodes were treated with elevated doses of oral MP (3 mg/kg per day) for 5 days at most.

Present prospective trial, triple drug-treated patients. From January 1986 to May 1987, at the same center, 128 consecutive cadaveric kidney transplant patients receiving first grafts were treated with triple drug immunosuppression during the first 10 weeks. CyA was initially administered in a dose of 10 mg/kg per day; it was later adjusted to whole blood trough levels of 400–800 ng/ml in the first 4 weeks and of 300–700 ng/ml thereafter up to 10 weeks, using the polyclonal Sandoz radioimmunoassay kit. Aza was given in a dose of 2 mg/kg per day and was then tapered to 1 mg/kg per day on day 14. The MP dose was initially 1 mg/kg per day, followed by 0.8 mg/kg per day on days 4–6 and 0.5 mg/kg per day on days 7–9; starting from the 10th day, the MP dose was 0.25 mg/kg daily.

After 10 weeks these patients, immunosuppressed initially with Aza, CyA, and steroids, were randomized into different treatment groups. This part of the study is, therefore, restricted to the first 10 weeks post-transplantation.

Treatment of acute rejection consisted of 3 mg/kg per day of oral MP for 5 days at most or 3 mg/kg per day antithymocyte globulin (ATG, Fresenius, Bad Homburg, FRG) for 3–8 days until transplant aspiration cytology became negative.

Monitoring

Monitoring of the patient and the graft. Fine needle aspiration biopsy (FNAB) of the historical controls was taken according to the protocol at least two times per week until day 25, when most of the patients were discharged from the hospital. The performance of FNAB and the preparation, staining, and evaluation of the smears have been described in detail elsewhere [5]. For the triple drug group, the protocol for taking FNAB was one to two times per week if graft function was good and serum creatinine was decreasing. If there were any clinical problems, or if inflammation or other pathological changes were present in the routine aspirate, biopsies were taken daily until the situation was resolved. All in all, the average frequency of biopsies in the historical controls was the same as that in the triple drug group.

An inflammatory episode was defined on the basis of inflammatory cell cytology in FNAB as a total corrected increment greater than 2.0, with over five tissue cells to guarantee the representativeness of the specimen. Rejection was defined clinically as an episode requiring additional immunosuppressive treatment. Rejection was diagnosed by clinical criteria, fever, tenderness and swelling of the graft, and an increase in serum creatinine.

Storage, documentation, and handling of the data. All information, including clinical data and the aspiration biopsy results, were stored and analyzed in a PDP 11/44 computer (Digital Equipment, Sunny Vale, Calif) using a modified MUMPS file manager program (G. Timpson, VA Hospital, San Francisco, Calif). Graft and patient survival are all actual. Statistical analysis was performed using the unpaired Student's t-test and chi-square test, when appropriate. Differences at the level of $P < 0.05$ were considered significant.

Table 1. Characteristics of patients and transplants on entry. * $P < 0.01$ (compared to triple drug group)

	Historical controls			
	Group A Aza + MP ($n = 32$)	Group B CyA ($n = 32$)	Group C CyA + MP ($n = 32$)	Triple drug group Aza + MP + CyA ($n = 128$)
Age (years)	43 ± 12	43 ± 14	42 ± 12	46 ± 12
First grafts (%)	75	78	83	100
Primary renal disease (%)				
Glomerulonephritis	41	44	56	32
Diabetic nephropathy	13	19	16	21
Preoperative dialysis treatment (%)	87*	79*	84*	100
Hemodialysis	56	41	59	54
Peritoneal dialysis	31	38	25	46
Time in dialysis (months)	16 ± 17	11 ± 11	13 ± 11	13 ± 13
Weight/height ratio (kg/cm)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
Histocompatibility				
AB mismatches	1.5 ± 0.8	1.6 ± 0.9	1.5 ± 0.6	1.5 ± 0.7
DR mismatches	1.1 ± 0.6	0.9 ± 0.8	0.9 ± 0.6	0.9 ± 0.7
Preformed antibodies				
No preformed antibodies (%)	58*	59*	69*	88
Mean ab reactivity, peak serum	20% ± 28%*	15% ± 26%*	18% ± 20%*	5% ± 16%
Average number of transfusions	10 ± 11	9 ± 13	11 ± 13	7 ± 9
Cold ischemia (hours)	35 ± 8	34 ± 9	35 ± 8	30 ± 7

Table 2. Episodes of inflammation during immediate postoperative period. * $P < 0.01$; ** $P < 0.001$ (compared to triple drug group)

	Number of inflammatory episodes per patient in group	Day of onset of inflammation per patient with inflammation[b]	Mean duration of all inflammation per group (days)	Peak intensity of inflammation in patients with inflammation (Cl-units)
Triple drug group (0–30 days)				
Aza + CyA + MP	0.8 ± 0.8[a] (*n* = 128)	10.1 ± 5.5 (*n* = 81)	2.7 ± 3.8 (*n* = 128)	5.5 ± 2.9 (*n* = 81)
Historical controls (0–25 days)				
Aza + (high initial) MP	1.3 ± 0.7* (*n* = 32)	9.4 ± 4.0 NS (*n* = 28)	7.8 ± 6.9** (*n* = 32)	6.1 ± 2.4 NS (*n* = 28)
CyA	1.7 ± 0.9** (*n* = 32)	6.1 ± 2.9** (*n* = 31)	11.7 ± 6.2** (*n* = 32)	7.2 ± 2.9 NS (*n* = 31)
CyA + (high initial) MP	1.6 ± 0.9** (*n* = 32)	9.8 ± 4.8 NS (*n* = 28)	8.6 ± 7.7** (*n* = 32)	5.6 ± 2.6 NS (*n* = 28)

[a] Mean ± SD
[b] Inflammation defined as > 2.0 corrected increment (Cl) units

Table 3. Episodes of rejection during immediate postoperative period. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (compared to triple drug group)

	n	Number of patients with rejection[a]	Number of rejection episodes per patient	Day of onset of rejection in patients with rejection	Duration of all episodes of rejection per patient with rejection (days)	Duration of all episodes of rejection per group (days)
Triple drug group (0–30 days)						
Aza + CyA + MP	128	26[b]	0.2	15.2 ± 8.1 (*n* = 26)	6.0 ± 2.3 (*n* = 26)	1.1 ± 2.7 (*n* = 128)
Historical controls (0–25 days)						
Aza + (high initial) MP	32	24	0.8***	9.8 ± 5.5**	5.5 ± 3.8 NS	4.3 ± 4.4***
CyA	32	27	0.8***	7.7 ± 4.7***	8.1 ± 3.5*	6.5 ± 4.5***
CyA + (high initial) MP	32	26	0.8***	11.7 ± 7.4 NS	6.6 ± 3.5 NS	5.5 ± 4.2***

[a] Rejection defined as an episode requiring additional immunosuppression
[b] 26 patients with 30 episodes

Results

Characteristics of the patients

Characteristics of the patients, both historical controls and patients in the prospective, triple drug treatment study, are given in Table 1. Historical controls included, on the average, 20% second allografts, whereas all patients in the triple drug group received first grafts. In addition, historical controls had more preformed antibodies and about 20% of them had received no preoperative dialysis treatment. Aside from this, however, there were no significant differences with regard to any of the tested parameters, either within the historical groups or between these and the prospective, triple drug-treated patients.

Episodes of inflammation during the immediate postoperative period

Frequent FNABs were performed to monitor inflammatory episodes in the transplant during the immediate postoperative follow-up of 25–30 days. These results are summarized in Table 2.

On the average, 0.8 inflammatory episodes, defined by more than 2.0 corrected increment units in graft cytology in two or more consecutive biopsies, were recorded per patient under triple drug treatment. This was significantly less than that recorded in historical controls, i.e., the 1.3 episodes in patients receiving Aza + MP ($P < 0.01$), the 1.7 in patients receiving CyA ($P < 0.001$), and the 1.6 in patients receiving CyA + MP ($P < 0.001$).

Under triple drug treatment the inflammation commenced, on the average, on day 10. This was not significantly different from when it commenced in historical controls receiving Aza + (high initial) MP (day 9.4) or CyA + (high initial) MP (day 9.8); it was, however, later than in patients receiving CyA monotherapy (day 6.1 post-transplantation; $P < 0.001$). Considering the whole prospective cohort, the mean duration of inflammation was significantly shorter in triple drug-immunosuppressed patients (2.7 days) than in historical controls (7.8–11.7 days; $P < 0.001$). However, there were no significant differences in the peak intensity of inflammation in corrected increment units in those patients undergoing an inflammatory episode.

Rejection episodes are presented in Table 3. Significantly fewer episodes of rejection – 0.2 per patient – were recorded in triple drug-treated patients during the first 30 days after transplantation than in historical controls – 0.8 episodes per patient in each group ($P < 0.001$). The first rejection episode in the triple drug-treated group also commenced later, on the average on day 15.2 as compared

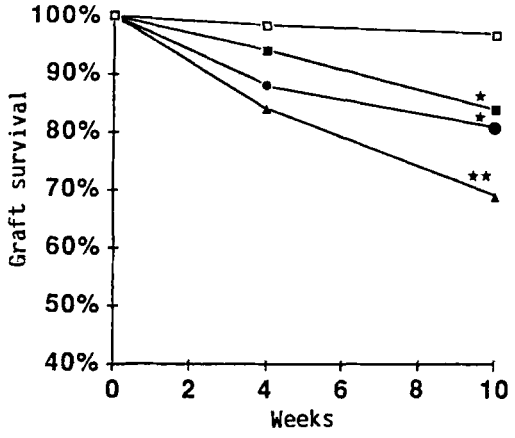

Fig. 1. Graft survival (curves are actual; chi-square test used for intergroup comparisons). * $P < 0.01$; ** $P < 0.001$ (compared to prospective trial). □, Triple drug group (prospective trial); ■, CyA + MP (retrospective controls); ●, Aza + MP (retrospective controls); ▲, CyA (retrospective controls)

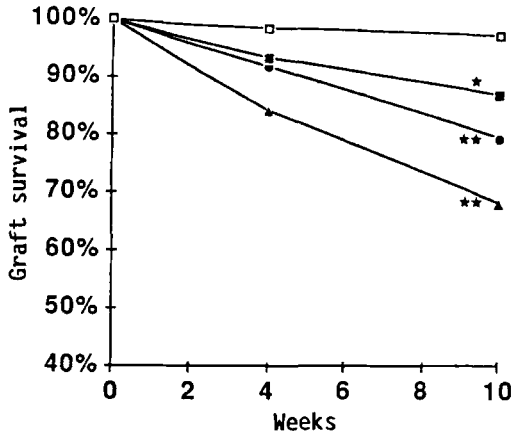

Fig. 3. First graft survival (curves are actual; chi-square test used for intergroup comparisons). * $P < 0.05$; ** $P < 0.001$ (compared to prospective trial). Symbols as for Fig. 1

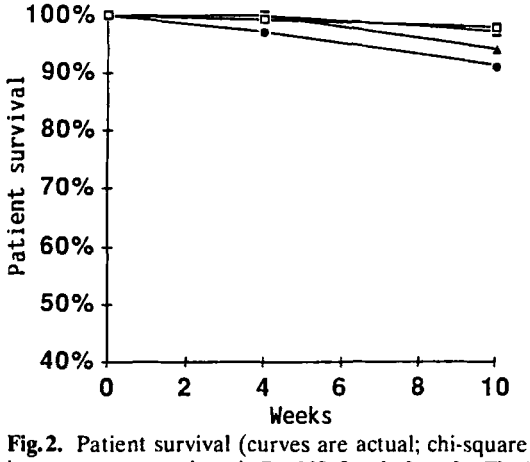

Fig. 2. Patient survival (curves are actual; chi-square test used for intergroup comparisons). P = NS. Symbols as for Fig. 1

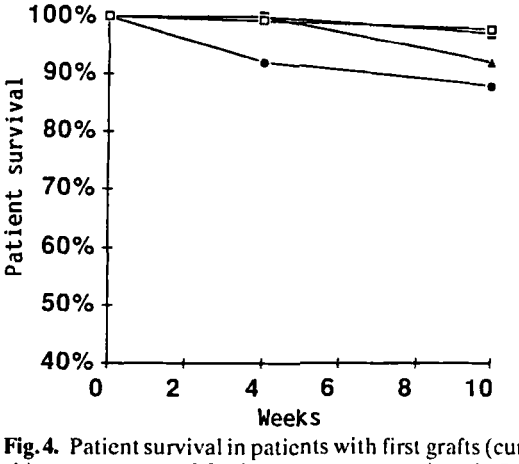

Fig. 4. Patient survival in patients with first grafts (curves are actual; chi-square test used for intergroup comparisons). P = NS. Symbols as for Fig. 1

to day 7.7–11.7 in the historical controls. On the other hand, there was no difference in the duration of rejection in patients undergoing a rejection episode; rejection lasted for 6.0 days in patients who were triple immunosuppressed compared to 5.5–8.1 days in historical controls. Considering the group as a whole, however, significantly fewer days were recorded during which triple drug-treated patients experienced rejection than during which controls did (1.1 day per patient vs 4.3–6.5 days per patient, respectively; $P < 0.01$).

Actual intake of drugs

We also analyzed, in retrospect, whether the patients had actually received the medication planned at the beginning of the trial. The intake of Aza was comparable in group A and in the triple drug group, as was the intake of CyA in groups B and C and in the prospective cohort. Differences were, however, revealed in the intake of steroids. In group C, after 10 days, only six patients (19%) were off steroids as planned in the protocol; after 25 days this was true of eight patients. In group B, CyA monotherapy, the patients were unable to go without steroids; after 10 days as many patients in this group as in group C were using MP, and after 25 days 20 patients needed MP. After 1 month, the consumption of MP was equal in all historical groups. At the beginning of the study, grafts were lost to acute rejection on CyA monotherapy, causing a change in treatment policy. In groups B and C, after rejection treatment MP was continued in low doses, for fear of underimmunosuppression on CyA monotherapy alone.

Graft and patient survival up to 10 weeks

Graft and patient survival in triple drug-treated patients and in historical controls are given in Figs. 1 and 2 and in patients in the same groups with first grafts in Figs. 3 and 4. The causes of graft and patient losses are given in Table 4. Under CyA monotherapy, five grafts were lost to acute rejection, while none in the triple treatment group was lost during the 1st weeks. Four of the 128 grafts were lost in the triple drug group – 1 because of a primary nonfunctioning

Table 4. Causes of death and graft loss according to treatment group during the first 10 weeks

	Group A Aza + MP ($n = 32$)	Group B CyA ($n = 32$)	Group C CyA + MP ($n = 32$)	Triple drug group Aza + MP + CyA ($n = 128$)
Causes of death				
Infection	2	1	1	1
Cardiovascular	1	1	–	1
Rupture of aortic aneurysm	–	–	–	1
Total	3	2	1	3
Causes of graft loss				
Rejection	2	5	1	–
Primary nonfunctioning graft	–	1	1	1
Rupture of graft with rejection	–	1	–	–
Arterial occlusion	–	1	1	–
Surgical complication	1	–	–	–
Other	–	–	1	–
Total	3	8	4	1
Total losses	6	10	5	4
Graft survival (10 weeks)	81%	69%	84%	97%
Patient survival (10 weeks)	91%	94%	97%	98%

Table 5. Graft function and cyclosporin concentrations at 1 month. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (compared to triple drug group)

	Group A Aza + MP	Group B CyA	Group C CyA + MP	Triple drug group Aza + MP + CyA
Creatinine (μmol/l; mean ± SD)	189 ± 81	291 ± 143***	281 ± 178**	168 ± 90
Creatinine clearance (ml/min)	41 ± 31	27 ± 18***	34 ± 18***	51 ± 21
CyA concentration (ng/ml)	–	180 ± 52[a]	169 ± 63[a]	588 ± 250[b]
CyA dose (mg/kg)	–	8.6 ± 1.7	8.8 ± 2.7	8.3 ± 2.7
Urea (mmol/l)	20 ± 11*	31 ± 20***	23 ± 15*	14 ± 8

[a] Serum
[b] Whole blood

kidney and 3 because the patients died with functioning grafts – giving a graft survival of 97% and a patient survival of 98%. There were no statistically significant differences in patient survival among the four groups of patients, either with regard to all patients or to those with first grafts only. Graft survival for first grafts at 10 weeks postoperatively was 79%, 68%, and 87% for groups A, B, and C, respectively, and graft survival including second grafts was 81%, 69%, and 84%, respectively. There were statistically significant differences in graft survival between the triple drug-treated patients and the various historical control groups (group A $P < 0.001$, group B $P < 0.001$, group C $P < 0.05$) for first grafts.

Graft function

Table 5 shows graft function tests and CyA concentrations in graft recipients at 1 month. Serum creatinine and urea values were significantly lower in triple drug-treated patients and creatinine clearance higher than in patients receiving CyA or CyA and steroids, regardless of an equivalent CyA dose. The CyA concentrations were difficult to compare, as two different methods of measurement were used. Graft function tests of historical controls at 10 weeks were not sufficient to allow for any comparison.

Discussion

The serious bias in this study was that we had to employ historical controls. These historical controls were transplanted, on the average, 3.5 years earlier at the same institution. This was, however, necessary since randomization of patients into four initial groups with 128 patients in each was obviously impossible in a single center study. Moreover, it was considered unethical to employ only Aza + MP or CyA monotherapy in 1986 for cadaveric renal transplant recipients.

Nor were patients in the experimental group and the historical controls entirely identical in their backgrounds. There were approximately 20% second allografts among the historical controls and the historical recipients also had preformed antibodies more often than patients in the triple drug group (approximately 30% of all controls compared to 10% of the latter). In these respects, there is a minor bias towards the triple drug group and against the historical controls.

The FNAB follow-up time for historical controls was 25 days, compared to 30 days in the prospectively investigated triple drug patients. The protocols for taking FNABs were also slightly different. In practice, however, the FNABs in all four groups were taken at the same frequencies. In these respects, the minor bias is towards the historical controls and against the triple drug group.

In the short run, triple drug treatment was obviously advantageous when compared to either of the double drug or single drug protocols. The frequency of inflammatory episodes, which is a parameter independent of clinical evaluation, and the frequency of clinical rejection episodes in the triple drug recipients were significantly lower than in any one of the historical control groups. Moreover, whereas the first episode of inflammation of the graft commenced simultaneously in the triple drug group and in two of the control groups, the onset of clinical rejection in the triple drug group was obviously slower, as rejection, requiring treatment with extra immunosuppression, was recorded on the average 5 days later in the triple drug-

treated patients. Thus, taking each group individually, grafts were inflamed and patients were treated for rejection significantly fewer days under triple drug treatment than in any one of the control groups. On the other hand, once inflammation commenced, there were no differences in peak intensity of inflammation between patients in any one of the four groups.

Graft and patient survival at 10 weeks, and the reasons for graft loss prior to this point, provide some additional information. There were no obvious differences in patient survival. On the other hand, graft survival rates clearly favored the triple drug-treated patients over controls at 10 weeks ($P < 0.01$ for groups A and C and $P < 0.001$ for group B). No grafts in the triple drug-treated group were lost to rejection during the first 3 months, and there were no more fatal infectious or other complications under more intensive immunosuppression. On the other hand, this point in time was too early to reliably analyze the frequency of cytomegalovirus infection under increased immunosuppression.

With regard to graft function, creatinine, urea, and creatinine clearances were better in the triple drug-treated patients at 1 month than in controls. At the same time, the CyA dose per kilogram body weight was the same for each CyA treatment group. During 1981 and 1982, CyA concentration was assayed from serum, while in 1986 it was measured from whole blood. Thus, these parameters were not comparable. As rejection frequency was significantly higher in the control groups, impairment of graft function at 4 weeks may have depended on more frequent episodes of rejection. After rejection, grafts may become more susceptible to CyA toxicity.

Taken together, it seems that the short-term results of the triple drug treatment were at least equal to, if not better than, those under any one of the double drug combinations or those under CyA alone. Because of the retrospective nature of the controls, it was not possible to provide definitive proof of this point in this study.

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