

## SURGICAL PROCEDURES NOT CONNECTED WITH TRANSPLANTATION IN PATIENTS AFTER KIDNEY OR KIDNEY AND PANCREAS TRANSPLANT WITH STABLE FUNCTION OF GRAFT\*

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**The aim of the study** was to evaluate complication during and after surgical procedure without connection with transplantation among patients after kidney, kidney and pancreas transplantation with stable function of graft.

**Material and methods.** 54 patients underwent 62 surgical procedures without connection with transplantation procedure. Main characteristic: standard immunosuppressive treatment, main age  $51.1 \pm 13.95$  years, men 77.4%, hospitalization time  $5.27 \pm 3.31$  day, group 1 – 55 procedures among patients after kidney transplantation, group 2 – 7 procedure among patients after kidney and pancreas transplantation.

**Results.** Procedures from general surgery comprised 60% [cholecystectomy 19 (51%), left hemicolectomy 1 (3%), esophagus removal 1 (3%), hernia repair 8 (22%), nephrectomy 3 (8%), pancreas transplantation in patients with functional renal graft 1 (3%), laparotomy 4 (11%), vascular surgery 27% (correction of arteriovenous fistula 13 (76%), by-pass surgery 1 (6%), embolectomy 1 (6%), implantation of aortal – iliac stentgraft 1 (6%), surgery of iliac artery 1 (6%)]. There has been no difference between parameters measured before and after procedure: creatinine ( $p=0.93$ ), GFR ( $p=0.07$ ), urea ( $p=0.25$ ), glycaemia ( $p=0.322$ ), glycated hemoglobin ( $p=0.3$ ), C-peptide ( $p=0.3$ ). In both groups were no differences in levels of creatinine ( $p=0.78$ ) and urea ( $p=0.23$ ), measured in the next years after surgical procedure. Mortality 0%, lost of graft 0%, in – hospital morbidity 10 (16.2%) (hematoma 1.6%, endocavitary electrode 1.6%, wound healing defect 16.2%). Morbidity in group 1 – 12.7%, group 2 – 48.8%,  $p=0.04$ .

**Conclusions.** Surgical procedures performed in a specialist center do not impair prognosis of patients with stable function of graft, after kidney, kidney and pancreas transplantation.

**Key words:** kidney transplantation, kidney and pancreas transplantation, complication

It is commonly believed that surgical procedures – in particular laparoscopic ones in patients after organ transplantation, on immunosuppressive treatment, undergoing multiple procedures, are connected with higher risk than general population. There are numerous literature reports on hernia repair and cholecystectomy in transplant recipients (1, 2, 3). However, there are no randomized studies on general surgical procedures.

The aim of the study was to evaluate complications during and after surgical procedures not connected with transplantation in patients after kidney or kidney and pancreas transplantation with stable function of graft.

### MATERIAL AND METHODS

The study comprised patients who underwent organ transplantation in the Central

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Hospital of Internal Affairs and Administration Ministry in Warsaw before 2010. Patients who were lost from follow up in our center were not included in the study.

From among 255 patients after kidney or kidney and pancreas transplantation, followed up in the Transplantologic Outpatient Office, CSK MSWiA in Warsaw, 54 patients (21.2%) were selected, in whom 62 surgical procedures not connected with the graft were performed, which constitutes  $1.15 \pm 0.45$  procedures per patient. In this group of 54 patients, there were 7 recipients of kidney and pancreas graft.

All patients received immunosuppression according to current standards; kidney transplant recipients received cyclosporin (CsA), mofetil mycophenolan (MMF) and glucocorticoids (GS), and patients after kidney and pancreas transplantation received tacrolimus (TAC), MMF and GS. They were characterized by stable function of the graft, i.e. with no signs of rejection.

All procedures were divided into 2 groups: group 1 – 55 procedures performed in patients after kidney transplant, group 2 – 7 procedures performed in patients after kidney and pancreas transplant.

## RESULTS

Mean hospital stay was  $5.27 \pm 3.31$  days. Mean age of patients was  $51.81 \pm 13.95$  years, with male

sex prevailing (77.4%). Patients from group 1 and group 2 differed significantly only in regards to age; patients who received renal and pancreas transplant were younger (tab. 1).

The patients underwent mainly general surgical and vascular surgical procedures. Most commonly it was cholecystectomy (30.6%) and hernia repair (12.9%), but also correction of arteriovenous fistula (17.7%), and other minor procedures. Among patients from group 1, one left hemicolectomy was performed due to adenocarcinoma, 3.5 years after renal transplantation. In the following 2 years no complications were observed in this patient. Also in patients from group 1 there was 1 esophagus resection due to cancer, 9 years after renal transplantation. There were no complications over 1 month of follow up in this patient. There was a difference in the number of laparoscopic cholecystectomies performed in both groups; the procedure was more common in patients from group 2 (16.3% vs. 42.9%,  $p=0.02$ ). The most frequent were inguinal hernias ( $n=4$ ), but also postoperative hernias ( $n=3$ ) and one scrotal hernia ( $n=1$ ). Corrective surgery of arteriovenous fistula was performed due to its dilatation – aneurysmatic ( $n=7$ ), hyperkinetic ( $n=1$ ) or variceal ( $n=1$ ), thrombosis ( $n=3$ ), and subsequent brachial artery aneurysm formation ( $n=1$ ) (tab. 2, 3 and 4).

During the surgical procedure – mean duration  $59.53 \pm 36.79$  min – none of the patients

Table 1. Basic characteristics

Feature	Study population n=62	Group 1 n=55	Group 2 n=7	p
Mean hospital stay	$5.27 \pm 3.31$ (dni)	$5.35 \pm 3.5$	$4.6 \pm 1.5$	0,97
Mean age of patients	$51.81 \pm 13.95$ (lata)	$53.3 \pm 13.8$	$38 \pm 6.6$	0,02
Sex	48 (77,4%)	43 (78,2%)	5 (71,4%)	0,67

Table 2. General surgical procedures

General surgical procedures	Study population n=62	Group 1 n=55	Group 2 n=7	p
Cholecystectomy	19 (30,6%)	15 (27,3%)	4 (57,1%)	0,1
Laparoscopic	12 (63,2%)	9 (16,3%)	3 (42,9%)	0,02
Left hemicolectomy	1 (1,6%)	1 (1,8%)	0 (0%)	0,7
Esophagectomy	1 (1,6%)	1 (1,8%)	0 (0%)	0,7
Hernia repair	8 (12,9%)	7 (12,7)	1 (14,3%)	0,9
Nephrectomy of own kidney	3 (4,8%)	3 (5,5%)	0 (0%)	0,5
Pancreas transplantation in patients with functional renal graft	1 (1,6%)	1 (1,8%)	0 (0%)	0,7
Laparotomy	4 (6,5%)	1 (1,8%)	3 (42,8%)	0,5

Table 3. Vascular surgical procedures

Vascular surgical procedures	Study population n=62	Group 1 n=55	Group 2 n=7	p
Correction of arteriovenous fistula	13 (17,7%)	12 (18,2%)	1 (14,3%)	0,79
Bypass surgery	1 (1,6%)	1 (1,8%)	0 (0%)	0,7
Embolectomy	1 (1,6%)	1 (1,8%)	0 (0%)	0,7
Implantation of aortal – iliac stentgraft	1 (1,6%)	1 (1,8%)	0 (0%)	0,7
Surgery of iliac artery	1 (1,6%)	1 (1,8%)	0 (0%)	0,7

Table 4. Other procedures

Other procedures	Study population n=62	Group 1 n=55	Group 2 n=7	p
Excision of skin lesion	5 (8,1%)	4	1 (14,3%)	0,5
Lymphocele puncture	2 (3,2%)	2	0 (0%)	0,6
Subcutaneous drainage	1 (1,6%)	1	0 (0%)	0,7

required blood products transfusion. Perioperative mortality was 0%.

The condition of patients after operation did not differ from that before the procedure, as reflected in both clinical examination and laboratory tests results. There was a statistically significant difference in systolic and mean arterial blood pressure and potassium level in perioperative period, but these values remained within the accepted range (tab. 5).

Hospital morbidity was 16.2%. It was usually connected with impaired wound healing, and was significantly more frequent ( $p=0.04$ )

in patients from group 2 (48.8%) than in those from group 1 (12.7%).

Follow up was on average  $5.85\pm 3.03$  years, it comprised all patients involved in the study. There were no deaths nor loss of transplanted organ within that time in patients who underwent surgical procedure not connected with transplanted organ (tab. 6).

There was no significant difference between the values of blood glucose, creatinine and urea in consequent years of follow up, which means that these parameters remained at stable levels (tab. 7).

Table 5. Tests results before and after operation

Feature	Before surgery	After surgery	p value
Ceatynine (mg/dl)	1,6 $\pm$ 0,7	1,67 $\pm$ 1,01	0,93
GRF (ml/min/1,73m <sup>2</sup> )	50,3 $\pm$ 19,2	53,29 $\pm$ 23,4	0,07
Urea (mg/dl)	58,1 $\pm$ 29,7	53,4 $\pm$ 31,2	0,25
Blood glucose (mg/dl)	107,6 $\pm$ 27,7	101,2 $\pm$ 33,2	0,32
Glycosylated Hb (%)	5,8 $\pm$ 0,25	6,35 $\pm$ 0,35	0,3
C-peptide	2,8 $\pm$ 0,2	1,9 $\pm$ 0,3	0,3
HCT (%)	37,7 $\pm$ 7,8	37,4 $\pm$ 7,4	0,53
RBC (*10 <sup>6</sup> / $\mu$ )	4,3 $\pm$ 0,9	4,2 $\pm$ 0,89	0,57
HGB (g/dl)	12,7 $\pm$ 2,6	12,6 $\pm$ 2,6	0,43
WBC (*10 <sup>3</sup> / $\mu$ l)	8,4 $\pm$ 3,8	8,1 $\pm$ 3,01	0,92
MCV (fl)	89,1 $\pm$ 5,6	89,4 $\pm$ 5,5	0,85
MCHC (g/dl)	33,8 $\pm$ 0,8	33,7 $\pm$ 0,95	0,78
MCH (pg)	30,2 $\pm$ 1,9	29,9 $\pm$ 2,2	0,97
PLT (*10 <sup>3</sup> / $\mu$ l)	222,4 $\pm$ 62,8	233,8 $\pm$ 82,8	0,33
Potassium (mmol/l)	4,6 $\pm$ 0,6	4,4 $\pm$ 0,47	0,026
Sodium (mmol/l)	137,4 $\pm$ 6,2	137,5 $\pm$ 4,04	0,59
Systolic blood pressure (mm Hg)	139,5 $\pm$ 22,5	131,3 $\pm$ 19,4	0,028
Diastolic blood pressure (mm Hg)	75,3 $\pm$ 11,9	73,6 $\pm$ 11,4	0,37
Mean blood pressure (mm Hg)	80,6 $\pm$ 38,5	75,4 $\pm$ 38,1	0,029

Table 6. Hospital morbidity

Feature	Study population n=62	Group 1 n=55	Group 2 n=7	p
Hospital morbidity	10 (16,2%)	7 (12,7%)	3 (48,8%)	0,04
Haematoma in operative wound	1 (1,6%)	1 (1,8%)	0 (0%)	0,7
Endocavitary electrode due to heart conduction abnormalities	1 (1,6%)	1 (1,8%)	0 (0%)	0,7
Impaired wound healing	10 (16,2%)	7 (12,7%)	3 (48,8%)	0,04

Table 7. Long-term observation

Observation period	Creatinine concentration in following years p=0,78	Urea concentration in following years p=0,23	Blood glucose in following years p=0,53
1 year	1,17±0,23	48,5±4,95	95,9±17,3
2 years	1,19±0,21	55±2,83	94±16,1
3 years	1,1±0,22	41,5±9,2	105,7±58,9
4 years	1,1±0,22	43,5±0,71	94,2±9,6
5 years	1,1±0,35	41±12,73	94,1±22,9
6 years	1,15±0,46	43±11,3	92,5±10,6
7 years	1,1±0,32	37±19,8	93±11,4
8 years	1,13±0,39	40,5±13,44	101,7±11,1

## DISCUSSION

Main adverse effects of immunosuppressive treatment is higher predisposition to neoplasms, but also infections and impaired wound healing (4). Delayed healing is in particular frequent in patients after transplantation, who are subjected to surgical procedures, but the most serious complication remains development of a neoplastic disease (5).

Among our patients, in 2 from group 1 operation not connected with transplanted organ was performed due to a neoplasm.

Occurrence of neoplastic processes in patients after renal transplant ranges from 2.3% to 31% and on average is 3 to 5 times higher than in the general population. Usually these are de novo neoplasms, in the form of skin cancer, non-Hodgkin lymphoma, Kaposi sarcoma, uterine cervix cancer in situ, anal and vulval cancer, primary hepatic cancer or cancer in patient's own kidney. Among these patients, persons receiving immunosuppression are exposed to higher risk of a neoplasm. It is well known that tacrolimus and cyclosporine, via increasing expression of TGF- $\beta$ , promote tumor invasion and metastases formation. Azathioprine stimulates carcinogenesis by inhibition of DNA thread repair. Polyclonal antibodies and monoclonal anti-CD3 antibody enhance development of skin cancer and posttrans-

plant lymphoproliferative syndromes. However, mycophenol acid, the precursor of which are mofetil mycophenolan and sodium mycophenolan, exert an antineoplastic effect by inhibiting adhesion molecules and limiting tumor dissemination. Similar effect show mTOR inhibitors, while basiliximab and daclizumab do not increase the risk of neoplasms (6).

The most common complication of surgical procedures in patients after organ transplantation, impaired wound healing, is connected with immunosuppression, in particular with sirolimus and everolimus, drugs from the group of early inhibitor of proliferation signal, as well as glyocorticosteroids (GCS) (7). In our study impaired wound healing was seen 16.2% of patients, and was significantly more frequent in those after kidney and pancreas transplant, as compared to patients who received only kidney graft. This may be connected with the dose of GCS. It has also been demonstrated that long term application of high doses of GCS may impair healing of intestinal anastomoses (8). The algorithms of immunosuppressive treatment for kidney transplant (CsA, MMF, GCS) or kidney and pancreas transplant (TAC, MMF, GCS), due to side effects of glyocorticosteroids, such as impaired wound healing, lipid profile abnormalities, arterial hypertension, pro-diabetic

effect, osteoporosis or obesity, suggest reduction of GCS doses, and discontinuation whenever possible (7, 9).

Among 10 patients with impaired wound healing it was most common after arteriovenous fistula (2 cases), hernia repair (2 cases) and cholecystectomy (2 cases). These procedures are most commonly performed in patients after organ transplantation and are widely discussed in literature. Cholecystectomy was performed in 30.6% of the studied patients, more frequently in kidney and pancreas recipients. There are reports in literature on the effect of immunosuppression, and especially cyclosporin, on the development of gallstones. It is connected with improper balance between deoxycholic acid and cholic acid, increased cholestasis and slower bile flow, but also glyocorticosteroids, which change the lipid balance (7, 10, 11). Due to these facts, and also potential infection in cholelithiasis, many authors claim that prophylactic cholecystectomy in asymptomatic patients before and after transplantation is justified. It also prevents cancer of the gall-bladder, the risk of which increases with gallstones and immunosuppressive treatment.

Our observations show that cholecystectomy, both laparoscopic and classic, in patients after organ transplantation is safe. It has been confirmed in many publications (2, 11-14). Hernia repair was performed as frequently in group 1 and 2. The most frequent (4 cases) were inguinal hernias. Hernia development is connected with risk factors such as immunosuppression, delayed function of the transplanted kidney, obesity, chronic respiratory tract diseases, diabetes and generalized infection.

Implantation of synthetic mesh is debatable, as it may constitute a potential source of infection, but significantly decreases the number of recurrences as compared with techniques involving tension (in abdominal surgery from 30-50% to 10%) (3, 15, 16, 17). The frequency of infection of implanted mesh ranges between 0.5% to 9%, and it may be limited by using new generation of mesh materials resistant to pathogens, as well as antibiotic perioperative prophylaxis in patients from high risk group. It seems that in predisposed persons, as for example with impaired immunity, prophylactic preoperative antibiotic administration, usually from cephalosporins group, is recommended (18). Some authors opt for laparoscopic repair of postoperative hernias, regarding it safe and effective alternative (1).

Among vascular surgical procedures, correction of arteriovenous fistulas were most frequent, mainly due to aneurismatic dilatation. In literature there are reports on aneurysms formation in dialysis fistulas, and on their impact on dilatation of brachial artery with time, and faster progression in patients with stable graft – by 10 mm per 10 years on average (19, 20). Arteriovenous fistulas which are not patent may give rise to neoplasms, including angiosarcoma, which makes their control mandatory (21).

## CONCLUSIONS

Surgical procedures performed in specialist centers do not worsen the prognosis of patients after organ transplantation (kidney, kidney and pancreas) on immunosuppressive treatment with stable function of graft.

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