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ORIGINAL ARTICLE

Autogenous transplants of adrenal fragments in an animal model

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: Adrenal insufficiency is a typical complication after surgical treatment of adrenal tumors, especially after the removal of both adrenal glands. Human beings are not able to survive without adrenal glands and without proper hormonal substitution. Autotransplantation of a fragment of the adrenal gland may prevent this complication. This can be done by transplanting the entire adrenal glands or its fragment, such as the adrenal cortex cells. In the case of adrenal tumors, the entire adrenal gland can not be transplanted. However, it is possible to transplant cells from the tumor-free part. Successful adrenal autografts may result in a new treatment of adrenal insufficiency.

Materials and Methods: Autograft transplantation was performed on 3 groups of Sprague Dawley rats. In the first group, physiological corticosterone concentrations were determined. These animals were not operated. In the second group, both adrenal glands were removed. Corticosterone concentrations were determined after bilateral adrenalectomy. The third group was divided into two parts. In the first subgroup, bilateral adrenalectomy was performed simultaneously with adrenal transplant into the omentum. In the second subgroup, right adrenalectomy was performed simultaneously with and adrenal transplant into the omentum followed a month later by left adrenalectomy. During the experiment, corticosterone concentrations were measured at 4 time points.

Results: The statistical difference between corticosterone concentrations in rats after two timed adrenalectomies and rats after bilateral adrenalectomy was statistically different, but these results were far from physiological concentrations.

KEYWORDS: grafts, transplantation, adrenal insufficiency, adrenal gland

INTRODUCTION

IAdrenal insufficiency is a notion that determines insufficient production of glucocorticoids, which may, but does not have to, be encountered together with insufficient excretion of mineralocorticoids and androgens. Most commonly, the predominant symptoms caused by adrenal cortex failure include fatigue, lack of appetite, abdominal pain, weight loss, orthostatic hypotension, increased craving for salt, and hyperpigmentation of the skin that occurs only with primary adrenal insufficiency.

Primary adrenal insufficiency, also known as Addison's disease, is a manifestation of primary adrenal diseases, at the basis of which in the past dominated tuberculosis and autoimmune syndromes nowadays. This sickness may also occur after surgery, as a result of metastases or in adrenal damage caused by medication. In the case of Addison's disease, the hypothalamic–pituitary–adrenal axis that regulated endocrine function of the adrenocortical cortex is not impaired.

A breakthrough in treatment of Addison's disease - adrenal insufficiency - took place in 1949 when synthesis of cortisone was discovered. Until that time, the disease was fatal. Substitutional treatment includes glucocorticoids and mineralocorticoids, often supplemented with sodium chloride. In the course of the disease, the patient must learn to assess his health condition and predict the demand for cortisone, which increases in situations of stress and disease. The patient must be able to perform intramuscular injection himself, bearing in mind the proper dose of hydrocortisone in case of an approaching adrenal crisis. Cortisone is secreted pulsatively, its highest concentrations are observed at morning hours, and lowest around midnight.

Both overdose as well as too small supply of steroids are incredibly common, particularly in stressful situations, in the case of an infectious disease or a sudden need for surgery. Lack of possibility to monitor proper dosage of steroids imposes additional difficulties. An excessive or insufficient supplementation of steroids may only be assessed on the basis of clinical symptoms. In excessive supplementation there is increase of body weight, insomnia, peripheral edema whereas in insufficient supplementation, lethargy, decreased appetite, and weight loss may be observed.

Despite treatment, quality of life and job opportunities are significantly reduced. A side effect of therapy is a series of sicknesses such as osteoporosis, obesity, diabetes and cardiovascular diseases. Often adrenal insufficiency is accompanied by affective disorder. Sexual needs are lowered due to lack of androgens. There is also considerable risk of premature deaths associated with adrenal crisis.

There is a great need for effective treatment of adrenal insufficiency. At present, hydrocortisone preparations with modified release are at the research stage; they allow to obtain a more stable concentration of cortisol that stimulates physiological levels of this hormone.

In the case of pheochromocytomas or other non-malignant tumors of the adrenal cortex with a well-defined border, there are treatments that save the adrenal cortex to avoid postoperative iatrogenic adrenal insufficiency.

Another direction of scientific research which is currently at an

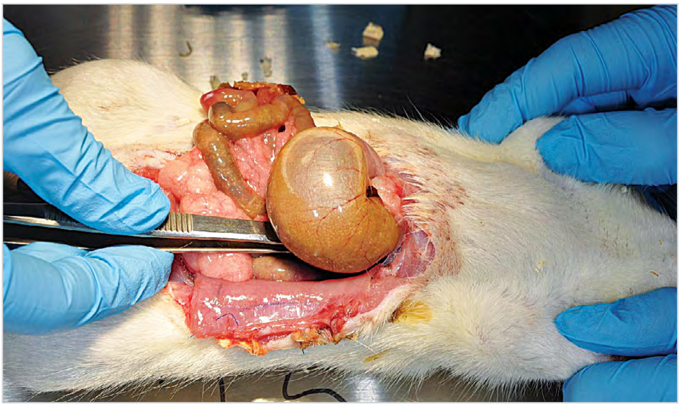

Fig. 1. Eventration.

Fig. 2. Transplant after the 56th day.

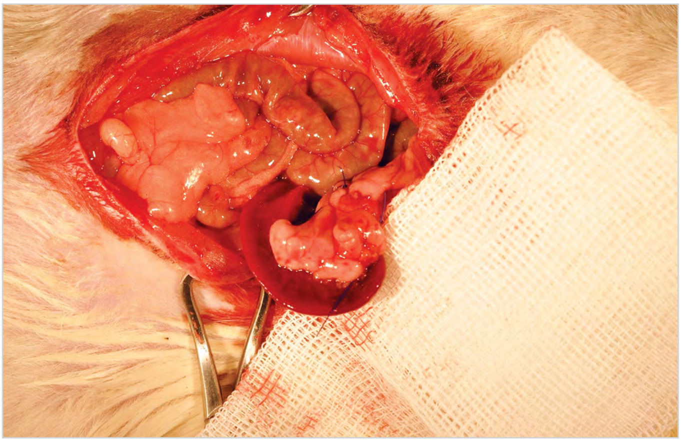

Fig. 3. Transplant in a larger network.

experimental stage in vitro and in vivo in an animal model are cell transplants. The basis of these scientific experiments is constituted by the ability of adrenal cortex cells to regenerate, proliferate and differentiate. There are two hypotheses explaining postnatal generation of zones in the adrenal cortex. The first was proposed by Salmon and Zwemer in 1941 with a model of centripetal migration . It is based around differentiation of undifferentiated progenitor cells from the pouch or subcapsular region into cells of the glomerular zone, which then migrate centrally and turn into cells of zona fasciculata producing glucocorticoids until apoptosis in the corticospinal link. Another hypothesis was made by Deane and Greep in 1946 and comprised a description of occurrence of zone-specific progenitor cells. Recent studies have shown radial nucleus/tract/band of progenitor cells that migrate from the glomerular zone into zona fasciculata Teebken and Scheumann have shown that transplantation of glomerular zone cells gives origin to cells of the glomerular zone and zona fasciculata.

Already in the 1960s, substitutional treatment was becoming the gold standard of treatment in hypothyroidism. Experimental autogenous adrenal transplantations in the thigh were performed in patients with Cushing's disease Only in the recent years attempts have been made to perfect allogeneic and xenogeneic transplantations, and stem cell therapy. Among the most interesting research one can mention studies by Hornsby et al., in which human or bovine cells of the adrenal cortex were transplanted to mice with severe combined immune deficiency (SCID). They showed that transplanted cells of the adrenal cortex are able to survive and create a functional tissue supplied with blood that may substitute the recipient organ, but only to the extent of glucocorticoids secretion This is associated with the discovery that cells of zona glomerulosa give origin to cells of zona fasciculata not only through biopotential progenitor cells contained therein, but also by way of conversion of the cell culture .

PURPOSE

The aim of my work is to examine undertaking of biological activity in the form of corticosterone secretion by autogenous grafts of the adrenal glands.

Assumptions: Proof for undertaking activity could contribute to changes in the current treatment of adrenal insufficiency, which at present is burdened with many side effects associated mainly with issues regarding dosage of these drugs. Treatment with adrenal grafts could eliminate many of these side effects because, contrary to exogenous hormones, transplanted adrenal gland fragments should function like normal adrenals and secrete hormones analogously to physiological adrenal glands.

MATERIALS AND METHODS

Rats

The experiment was conducted on 64 Sprague Dawley Rats from Animalab. All rats were mature males weighing over 450g (average weight at the beginning of the experiment was 498g). The animals were stored in single cages with soft wood lining under artificial lighting, cyclically switched off from 18:00 to 6:00. They were provided standard ad libitum feeding. All groups of rats except for the control group, in which no surgery was performed, were treated with 0.9% sodium solution to compensate for hyponatremia induced by adrenalectomy. This control group was given plain water.

Rats were divided into three groups, including two control groups, A and B, 8 rats each and one main group C consisting of 48 rats.

Control group A. No surgical intervention

The group consisted of 8 male Sprague Dawley rats with an average weight of 538g. The aim of the experiment in this group was to show physiological concentrations of corticosterone in rats subjected to repeated blood sampling. Blood was collected on days 1, 4, 28, and 56 to determine concentration of corticosterone. Rats were kept in conditions described above throughout the entire experiment.

Blood collection

A range of 0.5ml to 0.75ml of blood was taken into a sterile Eppendorf tube according to the procedure previously described by Furuham. Collection was carried out between 9 and 11 o'clock from tail veins in conscious rats after prior heating of the tail in a water bath at about 40°C. A 22G needle was used (0.7 x 40 mm). Blood was left for about 30 minutes at room temperature to form a clot, and then centrifuged for 15 minutes at 3500 rpm. The obtained sera were frozen until corticosterone was measured at -20°C.

Control group B. Bilateral adrenalectomy without transplant

The group consisted of 8 male Sprague Dawley rats with an average weight of 523g. Beside collecting blood done analogously to rats from control group A on days 1, 4, 28 and 56, bilateral adrenalectomy was done during day 2 of research. After surgery, rats were held in individual cages in conditions described above. They were given a 0.9% sodium solution. The experiment was aimed to show concentrations of corticosterone following bilateral adrenalectomy and confirm the ability of rats to survive without both adrenal glands.

Adrenalectomy, bilateral adrenalectomy, delayed adrenalectomy

Bilateral adrenalectomy was made in conditions of sterile (jałowy) operational block in a laying upright position. Animals were subjected to inhalational anesthesia with 5% Isoflurane. To maintain anesthesia, 2% -3% isoflurane was used. After shaving the stomach and using disinfectant on the skin, the abdominal cavity was opened with a median incision along the white line. Abdominal organs were shifted to the right side in an atraumatic manner to gain access to the left adrenal glands. After underpinning vessels reaching the left adrenal gland with a nonabsorbable monofilament suture size 4/0, the adrenal gland was gently removed along with a sustained capsule. Analogously, after atraumatic dislocation of abdominal organs to the left side and elevation of the lobe of the liver in such a way as to show the right adrenal, with particular attention given to the proximity of the liver and inferior vena cava, vessels reaching the right adrenals were underpinned and removed. After verification of homeostasis and making certain whether no adrenal residue has remained in the adrenal lodge, a double-layer suture (absorbable monofilament 4/0) was used to close the peritoneum. Furthermore, linea alba was closed with a continuous suture and the skin was closed with a single suture.

MAIN GROUP

The main group included 48 male Sprague Dawley rats with an average weight of 487.5g. All rats in this group were subjected to autogenous transplantations of adrenal fragments to vascularized tissues such as the omentum and abdominal muscles. This group was divided into two subgroups.

The first subgroup of 16 rats underwent two surgeries. On day 2, left-sided adrenalectomy with simultaneous transplantation of adrenal glands fragments was performed on the omentum majus and rectus abdominis muscle. Furthermore right-sided adrenalectomy was done on day 29 of the experiment. After surgery, rats were kept in individual cages in conditions described above and given a 0.9% sodium solution. Collection of blood was done analogously to control groups on days 1, 4, 28 and 56.

During day 2 of the experiment, the second subgroup underwent two procedures simultaneously; bilateral adrenalectomy with simultaneous transplantation of adrenal fragments to omentum majus and rectus abdominis muscle. After surgery, rats were held in individual cages in conditions described above and were given a 0.9% sodium solution. Collection of blood was done analogously to control group B in days 1, 4, 28 and 56.

Adrenalectomy, transplant of adrenal cortex fragments

The procedure was done in conditions of sterile (jałowy) operational block in a laying upright position. Animals were anesthetized via inhalation with 5% Isoflurane, and further with 2-3% during the procedure to maintain anesthesia. After shaving the stomach and applying disinfectant on the skin, the abdominal cavity was

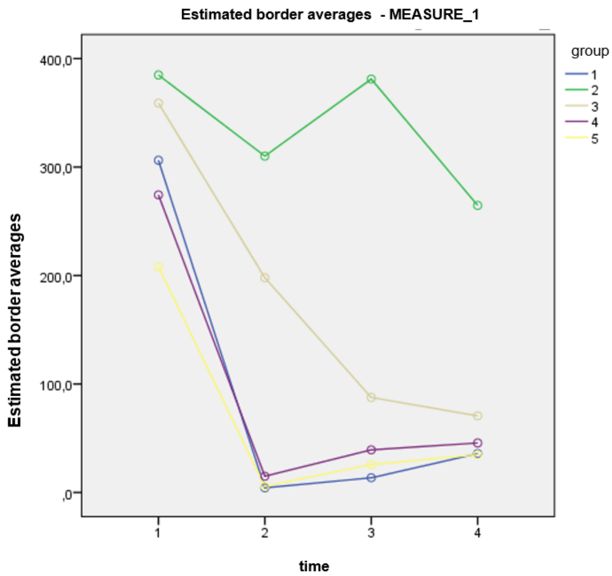

Fig. 4. Concentration of corticosterone in the following days of the experiment.

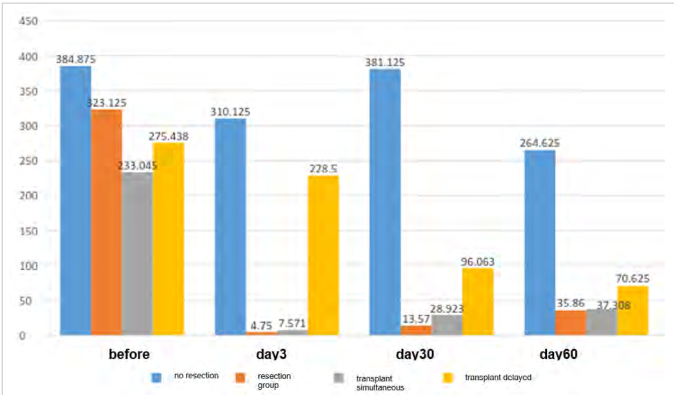

Fig. 5. Corticosterone concentration in subsequent days of the experiment depending on the group.

Tab. I. Subgroup 1. Twice operated. Histopathological result at the end of the experiment.

RAT NO.	TRANSPLANT
1	nerve trunks, hemosiderin deposits, scant inflammatory reaction
2	pancreatic fragment, inflammatory reaction with fine granulomas
4	5 pancreatic fragments with visible islets
5	pancreatic fragment with islets.
6	pancreatic fragment with islets.
8	pancreatic fragment with islets.
12	pancreatic fragment with a single islet.
14	pancreatic fragment. foci of encysted coagulative necrosis

Tab. II. Rats that survived till the end of experiment

RAT NO.	TRANSPLANT
*3	Adrenal gland (zona glomerulosa and zona fasciculata) 1 mm and pancreas
7	pancreatic fragments with islets.
9	pancreatic fragment with islets. histiocytic granuloma
10	fragment of normotypic pancreas, inflammatory reaction in submucosa
11	pancreatic fragment with islets. Epithelioid cell granuloma
13	pancreatic fragment with islets. granulomatous reaction
15	pancreatic fragment with islets scattered calcifications and granulomatous inflammatory reaction
16	pancreas with islets. two necrotic foci, granulomatous reaction around the periphery

opened with a median incision along the white line. Abdominal organs were shifted to the right side in an atraumatic manner to gain access to the left adrenal glands. After underpinning vessels reaching the left adrenal with a nonabsorbable monofilament suture size 4/0, the gland was carefully removed with a sustained capsule. In the first subgroup, the excised adrenal was cleaned of adhering tissues and chopped into very fine pulp on a sterile operating table. Material obtained in such a way was introduced into pouches made with purse-string suture in the omentum majus. After verification of homeostasis and making sure whether no adrenal residue has remained in the adrenal lodge, a double-layer suture (absorbable monofilament 4/0) was used to close the peritoneum. Furthermore, linea alba was closed with a continuous suture and the skin was closed with a single suture. (Fig. 3)

Next during day 28 in conditions of a sterile operational block with the use of inhalational anesthesia with Isoflurane, after opening the abdominal cavity following atraumatic dislocation of abdominal organs to the left side and elevation of the lobe of the liver in such a way as to show the right adrenal, with particular attention given to the proximity of the liver and inferior vena cava, vessels reaching the right adrenals were underpinned and removed. After verification of homeostasis and making sure whether no adrenal residue has remained in the adrenal lodge, a double-layer suture (absorbable monofilament 4/0) was used to close the peritoneum. Furthermore, linea alba was closed with a continuous suture and the skin was closed with a single suture.

The second subgroup had bilateral adrenalectomy on the second day of the experiment during which the adrenals were cleaned of surrounding tissues in sterile conditions. Next, they were shredded with a scalpel into very fine pulp and introduced into pouches made in the rectus abdominis muscle, closing the entrance to the pouch with a Z-suture.

On day 56 after collection of blood and euthanizing the rats, transplanted fragments were excised and sent for histopathological examination. (Fig. 2)

Serum samples were determined with an ELISA kit designed by DRG Instruments GmbH to determine corticosterone in mice/rats, which is a quantitative measurement method of corticosterone in rat serum.

RESULTS

Mortality

Overall mortality was 29 (45.3%).

In control group A it was 0 (0.0%).

In control group B it was 1 (12.5%). Death occurred on day 28 prior to third blood collection.

In the main group, it was 28 (58.3%).

In subgroup one operated twice, it was 9 (56.3%). All deaths occurred only after excision of the second, only physiological adrenal gland. Rats were awakened properly from anesthesia, however, death occurred within 24 hours of operation

In the second subgroup, mortality was 19 (59.4%). Two of these deaths occurred intraoperatively due to inferior vena cava damage. After surgery, all other rats were awakened properly, however, deaths occurred within 36 hours of surgery. Autopsy showed no obvious cause of death in the form of bleeding into the abdominal cavity or free fluid in the peritoneal cavity. Distended stomach and intestines were observed. There was wound dehiscence in 2 rats. (Fig.1)

Histopathological results of transplants

Subgroup one operated twice. (Tab.I)

Rats that died following the second surgery (Tab. II)

Subgroup operated once (Tab. III)

Corticosterone concentrations (Tab. IV)

Statistical evaluation of corticosterone concentrations (Fig. 4.)

- On day 1, corticosterone levels did not show statistically significant differences between groups.
- After bilateral adrenalectomy without a transplant, the control group shows no statistical differences in concentration of corticosterone between days 3, 30 or 60.
- In the group after simultaneous adrenalectomy, corticosterone concentrations are statistically increased in days 30 and 60 in relation to day 3.

- There were no statistical differences between corticosterone concentrations in days 30 and 60 in the group after bilateral adrenalectomy and in the group after bilateral adrenalectomy with simultaneous transplantation (Tab. VI).

DISCUSSION

Obtaining a functionally active adrenocortical cell transplant, analogous to allogeneic parathyroid grafts already in use, would probably allow to avoid overdose or insufficient supply of steroids in many situations. Transplants of fragments of parathyroid glands

do not currently involve complicated treatment. Previously prepared parathyroid cells are transplanted into the forearm under local anesthesia. This allows to withdraw from substitution treatment even for a few months, and at the same time immunosuppressive therapy may be avoided, the use of which brings a number of side effects .

The ability of adrenal cells to regenerate in vivo is a known process that has been proven in numerous studies. It is known that within 3-4 weeks of adrenal enucleation, during which there occurs damage of the cortex and medulla, there is fast growth and reconstruction of the adrenal cortex's structure and functioning. This process is stimulated with a significant increase of corticotropin concentration (ACTH), but also modulated by other substances such as N-POMC . It begins at the end of day 3 from enucleation with the proliferative phase . Thanks to stimulation of the progenitor cells located in zona glomerulosa, zona fasciculata is rebuilt by enucleation until day 20, whereas restoration of zona glomerulosa requires more time .

This process has been described only in case of adrenal enucleation in situ. Processes that take place in adrenal regeneration following transplantation of adrenal cells are far less known. Experiments in an animal model show partial reconstruction of the organ where a well-vascularized graft is created. An adrenal with proper layer construction was not obtained following transplantation. They show an impaired aldosterone and androgen production capacity, with almost normal glucocorticoid production.

Recently a case of an effective transplantation of numerous small adrenal fragments to the rectus abdominis muscle has been described in a kidney transplant from a family member. The graft functioned three years after transplantation. A number of tests were also carried out in an animal model. Allende described effective autogenous transplantation of the adrenal gland to the spleen. Concentrations of corticosterone on day 21 after transplant differed significantly compared to the group that underwent bilateral adrenalectomy but did not reach physiological concentrations. Till, on the other hand, performed adrenal cell transplants from rat fetuses to a network of larger adult rats and after 4 weeks performed bilateral adrenalectomy, following which he tested corticosterone levels for the next 6 months. He noted survival of transplants in 75% of rats and an increase in corticosterone to 70% of basal after 6 months.   Hornsby and his team made several models of xenogeneic transplants. He managed to transfer human adrenocortical cells under the renal capsule of SCID mice. In this experiment, prior to transplantation cells were grown for 5-7 days in vitro, and after transplantation the mice received exogenous steroids for 7 days. A vascularized graft that produced cortisol was obtained, the level of which reached a plateau between days 30 and 40. Hornsby underlines the role of 3T3 cell suspension in the induction of angiogenesis. Due to the difficulty in obtaining possible material for transplantation, a number of works emphasizes the role of progenitor cells which make it possible to obtain cell cultures that are an appropriate material for transplantation.

Tab. III. Subgroup operated once.
Histopathologies were collected only at the end of the experiment.

RAT NO.	TRANSPLANT
1	X
7	Inflammatory infiltrate from mononuclear cells with giant cells
12	X
21	1.5-mm adrenal surrounded by a thin layer of fibrous tissue with no signs of necrosis
22	Granulomatous reaction
23	Inflammatory granulation
24	Granulomatous reaction
28	Foci of inflammatory granulation
29	Granulomatous reaction
30	Granulomatous reaction
31	Granulomatous reaction
33	Granulomatous reaction
36	Granulomatous reaction

Tab. IV. Corticosterone levels.

AVERAGE NG/ML	BEFORE	DAY 3	DAY 30	DAY60
Without resection	384,875	310,125	381,125	264,625
Resection group	323,125	4,75	13,57	35,86
Simultaneous transplant with adrenalectomy	233,045	7,571	28,923	37,308
Transplants with delayed adrenalectomy	275,438	228,5	96,063	70,625

Most of the abovementioned authors emphasize the role of additional factors needed to perform an effective cellular transplant and proper preparation of material for transplantation in order to obtain a properly functioning graft. In the case of Balyura, it is the right number of cells in culture and a capsule of sodium alginate. This capsule reduces graft immunogenicity and constitutes a matrix. He showed that transplants of free cells underwent apoptosis and degradation faster and had shorter survival time. In Zupekan's studies, cells were enzymatically purified and then cultured and transplanted using a collagen matrix. Hornsby also purified cells needed for enzyme transplantation and then cultivated them in vitro for 5-7 days before transplantation. The cells were then transplanted in cylinders together with a 3T3 cell suspension that positively influenced the development of angiogenesis. In contrast, whole uncrushed adrenals were transplanted underneath the splenic capsule in Allende's experiments. According to many authors, postoperative hormonal supplementation allowing the cells to begin the proliferative phase within a few days after transplant is also significant. In above-mentioned experiments of the authors conducted in an animal model, adrenal cells were properly chemically purified and cultured in vitro for a few days.

CONCLUSIONS

Life grafts were found in only 2 rats during histopathological examination, therefore effective adrenal transplants seem to be possible. However, corticosterone levels in the main group were significantly lower than physiological, therefore, the proposed transplant method is not effective. Cited authors emphasize the need to use additional factors that foster the adaptation of adrenal cells. Further research should attempt to find a factor increasing adherence of adrenal cells in the area of transplant.

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