

Negative Consequences of Fat Transplantation Enriched with Stem Cell Culture

(Literature Review)

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Abstract:

Throughout the history of civilization, methods for correcting defects in the human body have been developed and improved. In this regard, plastic surgery plays a special role. Its formation and development were not always accompanied by favorable outcomes of operations. In 1921, for the first time for aesthetic indications, liposuction (LS) was performed, aimed at correcting the shape of the lower legs. The course of the postoperative period was complicated by necrosis of the skin, then gangrene of the operated limb, which necessitated its amputation [1].

Introduction

In 1983, it was first proposed to use blunt cannulas for liposuction [2]. The report on the generally positive results of more than 3000 lipoaspirations, based on the results of observation of patients in the postoperative period, among other things, provides data on the main dangers and complications of drug therapy [2]. In modern surgical practice, liposuction is one of the most frequently performed cosmetic surgeries with various hardware techniques [3; 4].

In 2001, the discovery of mesenchymal stem cells (SCs) isolated from AHT was an important stimulus for the further development of autologous adipose tissue transplantation (AHT), including for aesthetic indications [5], and it was drugs that began to be used as the main method for collecting biological material for isolation of stem cell culture.

In 2008, fundamental studies of the unique regenerative properties of stem cells derived from AWT made it possible to introduce into clinical practice cell-coupled lipotransfer (CSL), a technique that can increase the volume of transplanted adipose tissue while minimizing the negative consequences of surgery [6].

As a rule, authors report positive results of the use of CSL in clinical practice [7–10]. In order to purposefully implement new cell therapy technologies in everyday activities, it is first necessary to identify their potential risks and complications; Therefore, it is necessary to critically analyze the experience of researchers who have specifically studied these aspects of medical activity.



Materials and Methods of Research

Negative consequences associated with CSL both at the stage of collecting biological material for the isolation of stem cells and at the stage of subsequent autoadipotransplantation can cause disability and pose a threat to life for practically healthy people. Without studying the results of the implementation of basic measures to prevent complications of CSL in the immediate and remote postoperative periods, this direction of plastic surgery is impossible in terms of its scientific justification.

The main purpose of the work is to assess the data of many researchers studying the possibilities of clinical use of SCs from VT on the safety of CSL at all stages of its implementation. A special incentive for collecting, processing and analyzing data from sources of scientific literature is the contradictory information of researchers who are purposefully engaged in the study of the problems of cell surgery from the standpoint of the application of its technologies within the framework of regenerative medicine.

Results of the study and their discussion

The clinical use of stem cells from adipose tissue is technologically carried out in several stages: 1) collection of biological material for the isolation of stem cells, carried out, as a rule, by liposuction; 2) direct separation of SC culture from AZT; 3) enrichment of the transplanted adipose tissue of the SC, its implantation in the zone of soft tissue deficiency of the human body during lipofilling [7–10]. Negative consequences of the clinical use of SCs from VT in plastic and reconstructive surgery can occur at any stage. According to existing data [11], at present, competent researchers have published about two dozen articles, in which almost 400 cases of CSL are performed, mainly with the aim of correcting the shape and volume of the mammary glands, eliminating deformities of the soft tissues of the face. An analysis of the content of the publications shows that the authors do not report any postoperative complications. The latter is probably due to the relatively small number of clinical observations, as well as the authors' careful adherence to the technologies used to perform this surgical intervention [11].

Regenerative medicine technologies in terms of cell therapy are not yet routine manipulations, but today some specialists in the field of plastic and reconstructive surgery selectively use them to correct defects in the soft tissues of the human body, as well as to treat complications of severe somatic diseases (coronary heart disease, diabetes mellitus, obliterating atherosclerosis of the vessels of the lower extremities). In general, drugs and lipofilling are integral parts of the stages of the application of cell technologies in plastic and reconstructive surgery. At the same time, the data published by the researchers do not allow us to conclude that liposuction and lipofilling are absolutely safe surgical interventions. The risk of complications in the postoperative period remains even when performing such operations in somatically healthy patients.

I. Negative Effects of Liposuction



Liposuction (LS) is one of the most common aesthetic surgeries in the world. The trend towards an increase in the frequency of its performance continues, so it is impossible not to take into account the opinion of the authors who report on the potential complications of drugs as one of the stages of CSL [12; 13].

In particular, there is evidence that the majority of specialists, considering drugs to be a minimally invasive and relatively safe intervention, perform this operation mainly on an outpatient basis, while the risks associated with the operation, especially in cases where it is performed to obtain AWT in order to isolate SC from it, are often underestimated by plastic surgeons [12]. According to different authors, the overall incidence of drug complications varies from 8.6 to 20%. The most common complications of drugs are: heterogeneity of the contour of the body surface (up to 20% of clinical cases), the formation of sulfuomas, hyperpigmentation of the skin in the area of removal of excess adipose tissue, various types of asymmetry of body shape, and the development of hypertrophic scars at the sites of cannula insertion [13; 14].

Fatal outcomes due to complications such as skin necrosis, development of generalized bacterial infections, necrotizing fasciitis (NF), pulmonary embolism (PE), and deep vein thrombosis of the lower extremities are recorded in 0.02–0.25% of cases [13; 15–17]. The postoperative mortality rate for drugs is 1 case per 5000 interventions [15].

Thus, despite the relative safety and minimal invasiveness of the drug, the performance of this operation, as well as other surgical interventions, is still associated with the likelihood of a number of complications. The overall frequency of complications during liposuction reaches 20% of all clinical cases, while fatal complications of this surgical intervention occur in 0.25% of cases.

1. Интраоперационные осложнения липосакции

A. Injuries to the anterior abdominal wall and abdominal organs

Despite the fact that the surgeon inserts the instruments no deeper than the subcutaneous layer of the anterior abdominal wall, a change in the angle of insertion of the device cannula into the adipose tissue, in combination with the anatomical features of the patient, in some cases can contribute to damage to deeper structures (muscles of the anterior abdominal wall, abdominal organs, etc.) [3]. Damage to the muscles of the anterior abdominal wall can subsequently lead to the formation of a hernial orifice with the eventual formation of an abdominal hernia.

A number of authors report cases of penetrating abdominal wounds during the performance of drugs of the anterior abdominal wall for aesthetic indications [18–21]. In particular, during LS, the walls of the intestines can be damaged, which causes the development of peritonitis, and in some cases, abdominal sepsis. Injury to the anterior abdominal wall or intestines during LS is the second most common cause of death (after thrombotic complications) during this operation [2; 22]. Some authors report damage to other internal organs, such as the gallbladder, pancreas, and spleen [12; 14].

Data on the case of successful treatment of disseminated peritonitis developed in a 52-year-old patient after performing drugs of the anterior abdominal wall are presented [23]. Symptoms of



discomfort in the abdominal cavity in the patient began to be detected within 48 hours after the drug (bloating, vomiting, lack of stool). The doctor of the clinic where the operation was performed recommended to increase the doses of analgesics. On the fourth day after the operation, infectious and toxic shock and abdominal sepsis were diagnosed. The patient was hospitalized in the intensive care unit of the general surgical hospital. After a short-term preoperative preparation aimed at stabilizing vital functions, a laparotomy was performed. Revision of the abdominal cavity revealed wounds of the small and large intestines, partial necrosis of the rectus abdominis muscle on the right, signs of diffuse purulent-fibrinous peritonitis. Small intestine resection, colon wound suturing, abdominal cavity sanitation and drainage were performed. The patient was in the intensive care unit for three weeks. In its treatment, staged debridement laparotomies were performed, during one of which a section of the intestine was resected with the formation of its junostomy and colostomy. Intestinal continuity is restored after 10 months. Subsequently, the patient underwent a number of reconstructive surgeries on the anterior abdominal wall with a positive outcome.

Special attention should be paid to cases of complications of liposuction performed for aesthetic indications. For example, a patient who came to the emergency department of a general surgical hospital seven days after the drug was reported [24]. During the examination in the emergency department, the patient complained of fecal discharge from the wound of the anterior abdominal wall (PBS). A CT scan of the abdomen revealed a PBS abscess, a colonic fistula that had formed and completely closed after the abscess was removed.

In general, cases of perforation of the anterior abdominal wall and injury of the abdominal organs during the performance of drugs, according to different authors, are extremely difficult for early diagnosis, since the clinical manifestations of the developed trouble in the abdominal cavity are masked by the pain syndrome after liposuction and are leveled by oral intake of painkillers for a certain time. Probably for the same reasons, in most cases, injuries to the abdominal organs during the performance of drugs are diagnosed by general surgeons, often more than 24 hours after the initial aesthetic surgery was performed.

Injuries to internal organs in the case of drugs are not always associated with technical defects in its performance. An important role in the development of these complications of operations can be played by the anatomical features of the patient's body structure. In order to timely detect such dangerous complications of liposuction as damage to internal organs, the plastic surgeon performing this operation must have sufficient knowledge of emergency surgery of the thoracic and abdominal cavities. He must timely suspect and diagnose a complication that has developed in the patient, and perform surgical intervention aimed at eliminating it.

C. Damage to blood and lymphatic vessels

Damage to small-diameter blood vessels is inevitable in LS. In this case, the probability of intensive bleeding is low, since it is successfully prevented by preoperative infiltration of subcutaneous fat with a solution containing vasoconstrictors, as well as the use of compression hosiery in the postoperative period [14]. In the absence of thorough hemostasis during surgery



or coagulopathies not detected before surgery, hematoma may form after LS in the surgical area [3; 25]. The formation of sulfuromas is the second most common complication after LS (2.3–3.5% of cases). As a rule, the cause of their formation after surgery is intraoperative damage to small lymphatic vessels [13]. For the same reason, LS of the anterior abdominal wall and pubic area may contribute to the formation of lymphoedema of the scrotum or labia majora [26]. In most cases, lymphoedema and seromas can be treated with compression hosiery and lymphatic drainage massage, but in the absence of a positive effect from conservative treatment, drainage of the formed cavity may be required [26].

C. Infectious complications of liposuction surgery

Since the destruction of adipose tissue in the area of its performance occurs to a certain extent during the drug, the formed biological environment is favorable for the vital activity and reproduction of microorganisms. In the absence of proper control over compliance with the rules of asepsis and antisepsis, various forms of purulent inflammatory phenomena can develop in the surgical area, ranging from superficial phlegmon to necrotizing fasciitis (NF), which is a life-threatening condition [27].

Bacteria (various types of streptococci, anaerobic and facultative anaerobic bacteria) are the most common pathogens of infections in the area of surgical intervention in drug therapy [28; 29], and sporadic cases of infections caused by mycobacteria (*Mycobacterium chelonae*, *M. fortuitum*, and *M. abscessus*) have been recorded [30–32]. In a number of publications, the authors report cases of local infection at the surgical site associated with contamination of the wound with *M. fortuitum* and *M. abscessus* [33].

In case of superficial phlegmon in the area of drug therapy, the purulent-inflammatory process is localized in the subcutaneous adipose tissue. Clinical diagnosis, as a rule, is based on the phenomena of fever, local hyperthermia, hyperemia, increased intensity of pain syndrome in the postoperative period, blood test results (increased levels of C-reactive protein and leukocytes), as well as characteristic CT signs (edema of the deep layers of the dermis, fascia, signs of regional lymphadenitis) [34–36].

A rare but often fatal complication of drugs is NF, a common purulent-necrotic process affecting the subcutaneous tissue, deep fascia, and underlying tissues. Cases of this complication are not routine in the practice of a plastic surgeon, but the development of this complication is often associated with an extremely high (up to 50%) risk of death [37–44]. CT is one of the most accurate methods for verifying NF, and the main criterion that distinguishes NF from superficial phlegmon is the presence of air bubbles in the underlying muscles [45]. In cases where a patient is diagnosed with NF, the method of choice is radical necrorectomy with adequate antibiotic therapy with an optimal infusion regimen [46].

Prevention of infection in the area of surgical intervention in the postoperative period, including in the case of drugs, is a medical problem. Since plastic and reconstructive surgeries with the use of cellular technologies, as a rule, are performed on patients against the background of existing comorbid pathology, the development of purulent-inflammatory phenomena in the area of the surgical wound cannot be regarded otherwise than as an unsatisfactory result of



CSL, which causes a deterioration in the patient's quality of life and irrational use of specialized health care resources. To prevent such complications, it is necessary to strictly follow the rules of asepsis at all stages of the patient's stay in the clinic, preoperative antibiotic prophylaxis of purulent-inflammatory complications for such patients even with minimal interventions.

II. Negative Effects of Stem Cell Culture Isolation from Adipose Tissue

Isolation of KS culture from autologous adipose tissue is a well-established medical technology. However, for its successful implementation and obtaining the appropriate amount of cell culture elements from the collected biological material, special knowledge and compliance with a number of technological features are required [52–62].

The properties of the excreted stem cells are influenced by the age of the patients, the nature of concomitant somatic diseases, and the anatomical and physiological features of the donor area used to obtain adipose tissue [52; 53]. In particular, it has been proven that the adipose tissue of diabetic patients, in contrast to healthy people, contains a smaller amount of stem cells, which are also characterized by a reduced phenotypic expression profile and the ability to proliferate [54].

The number and viability of SCs obtained from VT is largely influenced by the method of drug administration. In classical drugs, an increase in the level of negative pressure in the aspirator can adversely affect the number of polypotent cells released [55].

According to the recommendations developed in 2007, the lipoaspirate should be treated on the first day after the extraction of the biomaterial from the body, since the storage of the fat substrate removed during drug at room temperature is associated with a decrease in the survival potential of the stem cells [56].

In order to reduce the probability of microbial contamination of biological material and to exclude the possibility of tissue (non-cellular) contamination of the formed biological substrate, the fat layer remaining during the isolation of the SC culture is washed with a sterile solution of phosphate buffer with the addition of antibacterial and antimycotic agents [57; 58].

After lavage, VT is fermented with a sterile collagenase solution in order to release the components of the stromal vascular fraction (SSF) containing KS [59]. When isolating stem cells from VT, the authors pay special attention to determining the optimal timing of the enzymatic effect on lipoaspirate, since excessive excess of the duration of this process can lead to the destruction of the cell culture of the stem cells. A number of researchers recommend fermenting lipoaspirate for 1–2 hours [60]. It is believed that the enzymatic degradation of VT to a homogeneous lipoaspirate at a temperature of 37° C for two hours provides the best balance between the degree of dissociation of the initial biological material and the amount of SCs obtained [61].

Upon completion of the enzymatic cleavage of the lipoaspirate, the components of the SSF are centrifuged until the complete isolation of the lipoaspirate is carried out. The physical effects of centrifugation, as well as the pressure parameters of vacuum liposuction, can negatively affect the viability and amount of SCLTs used for cultivation [62].

III. Complications of lipofilling



The main method of transplantation of AWT enriched with KS culture is lipofilling (LF) or CSL. This operation is considered a relatively safe surgical intervention performed by plastic surgeons, including for aesthetic indications to correct the volume deficit of soft tissues of different anatomical localizations. When analyzing the scientific publications of many researchers, attention is drawn to the lack of reports on the complications of transplantation of FAT, enriched with KS culture, isolated from it. This circumstance may indirectly testify to both the relative safety of this operation and the lack of experience in performing such manipulations by specialists. At the same time, some authors provide data on the complications of lipofilling, a basic manipulation in AJT transplantation.

The negative consequences of LF include death, acute cerebrovascular accident, vision loss, surgical infections, and the formation of giant necrotic fat cysts [63–70]. For example, a group of researchers conducted a meta-analysis in 2015 and reported that life-threatening complications during lipofilling developed in 3.5% of cases, and the overall mortality rate after this manipulation was 0.3% [63].

At present, LF is often used for cosmetic indications to correct age-related involutive changes in the soft tissues of the face, as well as to correct the shape and volume of the mammary glands both in cases of their reconstruction and purely for aesthetic indications.

A number of authors report cases of blindness, acute cerebral circulation disorder, necrosis of the skin area in the area of surgical intervention during facial LF. In particular, information is provided on cases of vision loss by patients after performing lipofilling. As a rule, this complication developed when AVT was injected into the soft tissues of the nasal and periorbital regions with sharp needles [64–68].

Another complication of facial LF is skin necrosis at the site of injection of autologous adipose tissue. Most likely, this is due to embolization of small branches of the arteries that supply blood to the integumentary tissues at the surgical site [69].

The most common complication of LF, performed in order to correct the shape and volume of the patient's mammary glands, is the formation of fat cysts of different sizes in the postoperative period. Data are provided on three cases of detection of fatty cysts after breast augmentation by LF, which required surgical interventions to remove them with a generally positive outcome [70]. Enrichment of the transplanted adipose tissue of the stem cells makes it possible to prevent these negative results and reduce the likelihood of repeated surgical interventions aimed at removing cystic formations from the VT that have formed in the breast tissue after their LF [5]. The most severe and dangerous complications of lipofilling are the development of acute cerebral circulation disorder and vision loss. To prevent such negative phenomena, blunt cannulas should be used during AWT transplantation, rather than sharp needles, which, due to their technical features, are characterized by great opportunities for perforation of the artery wall. In addition, the maximum volume of the syringe for autoadipotransplantation into the soft tissues of the face should not exceed 1 ml. The volume of adipose tissue implanted with each pass of the cannula in facial LF should not exceed 0.1 ml, and in the paraorbital region should be less than 0.033 or 0.02 ml. anesthetic with the addition of epinephrine.



The development and implementation of cell technologies in clinical surgery is encouraging. The possibilities of cell therapy are obvious, as well as the search for ways to modernize approaches to the performance of drugs and physical therapy, since today SCs from VT are used by doctors to treat such severe general somatic pathology as diabetes mellitus, obliterating diseases of the arteries of the extremities, and individual studies are aimed at improving heart function in a group of patients suffering from chronic heart failure. Of course, the possibilities of using stem cells isolated from autologous VT in clinical practice are closely related to the need to collect biological material for cell isolation, which is carried out mainly during liposuction with its subsequent implantation carried out during lipofilling.

Conclusion

The study of the sources of scientific literature allows us to consider that the production of biological material for the isolation of the culture of stem cells during liposuction has a number of features in comparison with drugs performed for purely cosmetic indications. First of all, during liposuction, adipose tissue is most often collected from patients suffering from concomitant general somatic pathology to a certain degree of severity and compensation for KS culture; Therefore, the examination of patients before surgery should be extremely thorough, and comorbid conditions should be adequately corrected with comprehensive therapeutic support of such patients. Particular attention should be paid to the prevention of complications both at the stage of collecting biological material for the isolation of stem cells and during its transplantation by lipofilling.

The possibilities of using cell technologies in clinical practice today are encouraging in the sense that many problems of plastic and reconstructive surgery can be solved using the properties of stem cells. However, the analysis of the data of many authors allows us to conclude that even with minimal invasiveness of surgical interventions at the stages of CSL, these operations are still characterized by a certain probability of complications, even in cases where they are performed in somatically healthy patients for aesthetic indications. Nevertheless, if a number of rules for performing operations using cell cultures are observed, there are still prospects for the successful use of cell therapy technologies and they cannot be denied. In order to prevent complications of CSL in the postoperative period, it is necessary to strictly follow the protocols of surgical interventions, carefully monitor the staff's compliance with the rules of asepsis and antisepsis, comprehensive prevention of thrombotic complications regardless of the extent of the operation, and targeted drug correction of the patient's concomitant general somatic pathology. Knowledge and implementation of a set of measures to prevent the negative consequences of transplantation of autologous adipose tissue enriched with stem cell culture should undoubtedly contribute to reducing the number of postoperative complications in cases of cell therapy in plastic and reconstructive surgery. The latter will ensure a wider introduction of innovative technologies of regenerative medicine into clinical practice.

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