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Contents of the Issue

i. Copyright Notice
ii. Editorial Board Members
iii. Chief Author and Dean
iv. Contents of the Issue

1. Iron Deficiency Anemia and Drug Addiction: Regional Problems and Ways of Solution. *1-6*
2. Ultrasound-Guided Femoral Nerve Block as an Anesthetic Alternative in the Management of Traumatic Injuries in Reconstructive Plastic Surgery in Heart Transplant Patients. *7-12*
3. Changes in Physical Qualities and Quality of Life after a Physical Conditioning Program in Hemodialysis Patients at the San José Renal Unit, Bogotá. *13-17*
4. Complex sSMC Involving X and Y Chromosomes in two Patients with 45,X/46,X,+mar Karyotype. *19-23*

v. Fellows
vi. Auxiliary Memberships
vii. Preferred Author Guidelines
viii. Index

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Iron Deficiency Anemia and Drug Addiction: Regional Problems and Ways of Solution

By Ne'matjon S. Mamasoliev, Burxonjon U. Usmonov & Xatam. X. Tursunov

Abstract- In general, the analysis of the available information in the modern literature shows that there is an increase of drug addiction occurences throughout the world. This increases social tension and arises medico-biological problems, in particular, related to early detection and therapy of CND (Chronic Non-communicable diseases) and IDS (Iron Deficiency Syndrome) amongst drug addicted population. The collected data emphasises the need to adjust the therapeutic or hematological work taking into account the growing tension in the narcological situation, which has already been formed on the basis of newly prioritized area - epidemiological narcology.

It is both interesting and logical to elucidate in an epidemiological study the characteristics of the response of the blood system during drug intoxication and to study the popular mechanisms of development of ID (Iron Deficiency), IDA (Iron Deficiency Anemia) and IDS with the background of drug addiction. Epidemiological, clinical and preventative aspects of the main risk factors for iron deficiency condition and associated pathological processes among drug-addicted population is the main discussion topic of our paper.

Keywords: *iron deficiency animia, epidemiology, risk factors, course, prevention.*

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Iron Deficiency Anemia and Drug Addiction: Regional Problems and Ways of Solution

Ne'matjon S. Mamasoliev [α], Burxonjon U. Usmonov [σ] & Xatam. X. Tursunov [ρ]

Abstract- In general, the analysis of the available information in the modern literature shows that there is an increase of drug addiction occurences throughout the world. This increases social tension and arises medico-biological problems, in particular, related to early detection and therapy of CND (Chronic Non-communicable diseases) and IDS (Iron Deficiency Syndrome) amongst drug addicted population. The collected data emphasises the need to adjust the therapeutic or hematological work taking into account the growing tension in the narcological situation, which has already been formed on the basis of newly prioritized area - epidemiological narcology.

It is both interesting and logical to elucidate in an epidemiological study the characteristics of the response of the blood system during drug intoxication and to study the popular mechanisms of development of ID (Iron Deficiency), IDA (Iron Deficiency Anemia) and IDS with the background of drug addiction. Epidemiological, clinical and preventative aspects of the main risk factors for iron deficiency condition and associated pathological processes among drug-addicted population is the main discussion topic of our paper.

It is a common knowledge that epidemiological and preventive studies are used to identify differences between country and population indicators in "reference groups" (countries or populations with a similar level of health indicators) and geopolitical groups (countries or populations united by geopolitics). This, firstly, makes it possible to find out the true epidemiological situations in relation to chronic diseases and, secondly, contributes to the development of effective preventative programs and/or shows possible ways of solving the epidemiological problems of non-infectious pathologies among various population groups [10,13]. Among the population, the most severe burden of CND is caused by such risk factors as AH (Arterial Hypertension), HCL (Hypercholesterolemia), HTG (Hypertriglyceridemia), HU (Hyperuricemia), BMI (Body Mass Index) , smoking, IBW (Increased Body Weight), Diabetes, CMD (Carbohydrate Metabolism Disorders), alcohol consumption, PI (Physical Inactivity), stress and hereditary factors [13,16,29,30,31,33, 34]. Another significant risk factors for drug addicted population are - an unsuccessful family factor, low consumption of vegetables and fruits, drug addiction, monotonous diet, strong tea / coffee consumption, nutritional factors, unfavorable social status, MTOs (microelementosis), medicinal factors, irregular nutrition, low educational status, polypathy, overeating and multiple risk factors [17,19,23,24,25,27].

It was found that some indicators have an increasing trend, others - decrease, and some others endure stabilization of the noted risk factors [14]. However, the mechanisms of the formation of the main risk factors for IDS in the amount of drug addicted populations have not yet been investigated in epidemiological studies. We came to this conclusion when analyzing data from a large stream of epidemiological and preventive studies, as well as available literature.

At the same time, it should be noted that in recent years, this problem has attracted attention of many researchers around the world [28,33,35, 38].

Keywords: iron deficiency animia, epidemiology, risk factors, course, prevention.

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I. Introduction

IDA - is a disease caused by the iron depletion in the organism and, according to WHO criteria, is manifested by a decrease in hemoglobin levels to less than 130 g / l in men and less than 120 g / l in women [8,35]. The clinical classification is based on the morphological principle - the determination of the mean erythrocyte volume (MEV), the coefficient of variation of the erythrocyte volume, ferritin concentration, hemosiderin deposition in the bone marrow, serum iron level, Total Iron Binding Capacity (TIBC) and hemoglobin level.

With iron deficiency, the entire body suffers, iron is absorbed in the duodenum and small intestine. For one meal, men absorb 1.3-1.5 mg, and women, despite the great need for "metal", only 0.3 mg. Regardless of gender, during the day a normal person loses (in the toilet rooms, with sweat and "dead" epithelium - the surface layer) about 1 mg of iron. During pregnancy, the need for it increases sharply, a woman needs 2.5-3.5 mg per day.

The body of an adult contains 3-4 g of iron. An important link in iron metabolism is its deposition. Violation of this process leads to the development of ID, mainly as a result of blood loss [7,30].

Iron deficiency in food rarely causes IDA in adults by itself, but contributes to its development in the presence of other Risk Factors . With a normal balanced diet, the human body receives 15-20 mg of iron per day, of which 5 to 10% is absorbed. Absorption increases up

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to 25% with ID in the organism. The percentage of iron absorption by the body also depends on the chemical structure of the substance in which it is included. So, gem iron (meat products, fish, poultry) is absorbed by 20-50%, the non-heme form of iron (cereals, vegetables, dairy products) is absorbed weaker, absorbed by about 5%. There are many factors on this process, as shown by some population studies. An increase in absorption is observed in the presence of ascorbic acid and a decrease is noted in the presence of acute and chronic inflammation [26,32].

II. Risk Factors and Course of IDS

According to the WHO, every 5th person on the planet is iron deficient, 30 percent of developing countries suffer from iron deficiency anemia. The main RFs of IDS NNS are: 1) chronic and acute blood loss (hyperpolymenorrhea, peptic ulcer of the stomach and duodenal ulcer, diaphragmatic hernia, esophagitis, erosive gastritis, Crohn's disease, diverticulosis, hemorrhoids, donation); 2) increased need for iron (during the growth of children and adolescents, pregnant and lactating women); 3) disorders of iron absorption in the small intestine, autoimmune atrophic gastritis; 4) alimentary factors (a decrease in the diet of foods containing iron. In the population of drug addicts, apparently, as sociological studies show, the range of RF of IDS is expanding.

So, in recent years, at the WHO level, it has been noted that from year to year the number of young people drinking increases, the amount of alcohol they consume and the frequency of its use increase, and the age at which young people start drinking is decreasing [4,22].

According to the above literature review by N.A. Nikiforova (1999), the anxiety about this is not accidental: • in Holland, 56% of adolescents aged 11 to 19 drink alcohol; • In France, 31% of boys and 15% of girls have a habit of drinking alcohol; • in Germany 45% of adolescents are threatened with alcoholism; • in Russia, by the age of 10, 12.1% of boys and 1.7% of girls are familiar with the taste of alcohol, and by the age of 17 - 47.2 and 31.4%, respectively; • 75% of boys and more than 50% of girls from vocational schools have experienced a state of intoxication, and 50% of boys and 20% of girls - repeatedly [15].

L.A. Atramentova (1991) investigated hereditary burden, the structure of parental marriages and marital selectivity of women suffering from alcoholism and drug addiction. The similarity of hereditary burden of both alcoholics and drug addicts was noted. The degree of exogamy of the parents does not affect the daughters' resistance to alcoholism and drug addiction [1].

According to the same study, in sick women with hereditary burdens, the likelihood of forming a married couple concordant for alcoholism and drug addiction is higher than in non-burdened women.

Research carried out by A.G. Soloviev et al. (1993) on 8 groups of 80 animals of white conventional male rats indicate that the change in a number of hematological parameters depends not only on the duration, but also on the nature of the alcohol-toxic effect. Under conditions of alcoholic toxicity, the number of erythrocytes and the total hemoglobin content is markedly reduced, which causes less and less erythrocytes in blood. The authors revealed a significant tension of erythropoiesis and erythrodieresis, which is, in general, an insufficient compensatory response to deep hypoxia. They expressed the opinion that the changes in the blood system caused by abovementioned process can, undoubtedly, be considered as one of the factors involved in the pathogenesis of narcological diseases [18].

G.M. Entin et al. (1999,2004) presents the following data on the prevalence of alcohol consumption among the population in recent years: alcohol consumption, which reached a maximum of 14.9 liters per capita in 1984, after the well-known measures to combat drunkenness and alcoholism (May 1985) decreased to 10 -11 liters per year (1986-88), but later, after the collapse of the Soviet Union, it began to grow again, reaching 15 liters in 1993-94 and stopped there for the next 10 years - until 2004 [22, 23].

The authors also wrote about the so-called "drug pyramid", although, according to the researchers themselves it is more like the Eiffel Tower in Paris. Nowadays in Russia there are 1.5-2 million drug users with the same situation, 90% of whom are heroin users [21, 23].

Similar judgments are expressed by other researchers regarding the high prevalence of drug addiction - a risk factor for CND in general and IDS in particular.

PC. Mustafetova (1996) showed that koknar drug addiction arises on the basis of cultural and ethnic tradition among the indigenous people of South Kazakhstan. The course of Koknara drug addiction is extremely slow and its development continues for decades. In women, the growth of tolerance to koknar is more than three times faster than in men. The author proposes the course of koknar addiction in 3 stages: the first stage is characterized by the manifestation of psychological and physical attraction; the second stage is characterized by the emergence of compulsive attraction and withdrawal symptoms, the third stage is characterized by the progressive desire of patients to indulge in the world of drug addiction dreams, the appearance of verbiage, vagrancy, loss of social ties with relatives and friends [14].

Consequently, in connection with the increase in recent years throughout the world, including in our

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republic, the frequency, firstly, of risk factors and, secondly, alcoholism and drug addiction, effective methods of epidemiological diagnosis and prevention of chronic diseases among the drug addicted population.

Researchers have confirmed that the health of citizens of Russia and the CIS has been deteriorating over the past 10-15 years [2]. This is explained by a number of circumstances: the collapse of the USSR, the unsettled and transparent borders between neighboring states, the economic and political reorganization of society, the redistribution of forms of ownership, the curtailment of state production, which led to unemployment, impoverishment, homelessness, an increase in crime and lack of spirituality. As a consequence, the threatening spread of RFs and bad habits such as alcoholism, tobacco smoking, prostitution and drug addiction and their abuse [11,12,13]. The very existence of a healthy lifestyle system, especially among drug addicted populations, is under threat, and therefore, in many regions, special programs have been created in the areas of prevention of chronic diseases and risk factors for their development, abuse of psychoactive substances and countering illegal drug trafficking.

Among many works in this direction, one can be singled out, which in 2003 for the first time in Russia on the basis of a representative sample in 13 constituent entities of the Southern Federal District (SFD) carried out a personal survey in order to assess the level of knowledge about their health, the harmful effects of drugs on the body. 7,800 people were tested - students and working youth aged 11 to 20 years.

The monitoring results show that at the age of 11, every second knows about the narcotic properties of cannabis or drugs of the opium group, at the age of 13 - already two-thirds, and by the age of 16 the share of children who are aware of drugs is close to 80%. Along with the consumption of narcotic drugs, the scale of the introduction of children and young people to the consumption of psychoactive substances such as tobacco products and alcoholic beverages is rapidly growing. In the age group 11-20 years, at least 50% smoke and consume alcohol, girls are increasingly involved in this category of young people. Consequently, it is necessary to regularly monitor the problems of substance abuse both in educational institutions and among the population with the systematization of educational and preventive work [2].

The extensive foreign literature devoted to the clinical, population and prophylactic aspects of drug addiction among the population, in general, is consistent with the above data and conclusions.

III. Results and Discussion

In the prevention of the spread of RF among the population, and especially of such bad habits as smoking, the use of alcoholic beverages and substances that cause substance abuse, the awareness of the population about their harmful effects on health is of great, albeit ambiguous, importance.

E.S. Skvortsova et al (2000) conducted an anonymous questionnaire survey of 4022 adolescents aged 15-17, high school students in Moscow secondary schools. The awareness of adolescents in relation to the harmful effects of psychoactive substances was revealed and the influence of such awareness on the behavior of adolescents was determined.

The results of the authors' study showed that along with the growing awareness of adolescents about the harmful effects of psychoactive substances, adolescents' use of these substances is spreading. At the same time, data have been obtained indicating the positive impact of awareness. It was noted that children and adolescents practically do not have reliable sources of information that take into account their age characteristics and use mainly “their own observations”, “their own experience” or receive information from adults [17].

In many works on the prevention of chronic diseases with the background of drug addiction, mainly social aspects were studied, and only relatively recently began to study medical and biological factors or personality traits, including the epidemiological and biochemical mechanisms of the development of non-infectious pathologies in drug addicts.

N.I. Ivanets, M.A. Vinnikova (1999,2001), characterizing the premorbid personality traits of heroin addicts, note that heightened excitability, a tendency to emotional outbursts with aggression, and protest reactions are detected already at the age of 4-6 years. Some of the patients had residual effects of organic diseases of the brain, most often suffered in childhood. Dysphoria with affective viscosity and stuckness was typical for them. A significant group consisted of people with hysterical character traits, with a predominance of asthenic and anxiously suspicious traits [11,12].

The risk groups for CND / IDS and the use of psychoactive substances include minors with a burdened heredity in terms of narcological and somatic diseases; with pronounced characterological, behavioral changes as a result of early or acquired organic cerebral pathology, with congenital or developing psychopathological traits due to defects in upbringing, pedagogically neglected and from socially disadvantaged families.

Brun E.I. et al. (2002), Bespalov A.Yu. et al. (1998), Davydkin I. (2009), Dumanyan D.T. et al. (2009) and many other researchers from non-CIS countries show that it is important to know not only the age of drug exposure, but also the environment (social, family, ecological and epidemiological), which provokes them and affects the formation of maladjustment. Preventive care should be addressed to a specific person [3,6,8,].

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In the process of the development of somatic pathologies, including IDS against the background of anesthesia, regardless of the type of drug used and premorbid characteristics, a "drug addict" personality is formed with its characteristic behavior and leveling of individual characteristics and the formation of a kind of drug addiction defect with increasing affective disorders in the form of dysphoric or anilitic abulic depressions, affective lability, the predominance of hysterically excitable forms of response, psychosocial dysfunction in the form of a gradual fading of interests, various anomalies of the emotional-volitional sphere, disorders of the sphere of drives, including sexual disinhibition [21,37,38].

According to many authors, hormonal levels are of great importance in the development and clinical manifestation of CND / IDS against the background of anesthesia [26].

The fact is that long-term abuse of surfactants causes secondary endocrine insufficiency, including adrenal insufficiency. Stimuli that cause clinical signs of sympathetic reactions, increased urinary excretion of catecholamines and plasma norepinephrine and epinephrine levels, include cold, pain, fear, exercise and anticipation of physical activity, hypoglycemia, hypoxia, hypercapnia, bleeding, fluid loss, drugs (anesthetic drugs) [39].

Psychosomatic manifestations of testosterone deficiency in men are characterized by poor mood, decreased physical and intellectual activity, irritability, and increased fatigue. Deficiency of estrogen in women is accompanied by memory impairment, decreased ability to concentrate, increased emotionality and severe depression. These conditions are risk factors, firstly, predisposition to the drug and, secondly, to the formation and aggravation of the course of CND, IDS and IDA in the drug addicted population [20].

The clinical picture of IDS among population with drug addiction is characterized with a significant severity of sideropenic (40.6%), anemic (30.6%) and "minor" symptoms from the nervous, cardiovascular and digestive systems (28.8%) leading to a decrease in working capacity and an increase in the tendency to faint. The greatest increase in the clinical manifestations of IDS occurs after 40 years.

Thus, the studies carried out in the population of drug addicts revealed a number of features of the formation of epidemiological and clinical conditions in relation to the development of CND and IDS, the assessment of the degree of which can be used in the population and clinical characteristics of the general severity of the patient's condition, as well as in the planning and implementation of preventive programs among drug addicted population with these pathologies.

Conflict of Interests and Contribution of Authors

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Ultrasound-Guided Femoral Nerve Block as an Anesthetic Alternative in the Management of Traumatic Injuries in Reconstructive Plastic Surgery in Heart Transplant Patients

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Summary- We present the clinical case of a 23-year-old male patient with a history of heart transplantation who suffered a bicycle accident presenting a bloody area in the left tibial region which was subjected to taking and applying a skin graft and allograft placement in a donor area under sedation. and ultrasound-guided femoral nerve block without presenting hemodynamic changes during the trans-anesthetic and adequate analgesia, resulting in a very useful alternative for this type of patients since they present physiological-anatomical changes after transplantation and it is required to maintain a hemodynamic state optimal to avoid perioperative complications.

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Strictly as per the compliance and regulations of:

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Summary- **We present the clinical case of a 23-year-old male patient with a history of heart transplantation who suffered a bicycle accident presenting a bloody area in the left tibial region which was subjected to taking and applying a skin graft and allograft placement in a donor area under sedation. and ultrasound-guided femoral nerve block without presenting hemodynamic changes during the trans-anesthetic and adequate analgesia, resulting in a very useful alternative for this type of patients since they present physiological-anatomical changes after transplantation and it is required to maintain a hemodynamic state optimal to avoid perioperative complications.**

I. Introduction

Christian Bernard performed the first human heart transplant in 1967. Currently, the average frequency of this procedure is approximately 1% of the population with heart failure. Heart transplantation is the definitive treatment of advanced heart failure and has been shown to improve results and long-term survival *(1, 4)*.

Currently, between 5000 and 1000 heart transplants are performed worldwide and this is increasing, on July 21, 1988, Dr. Rubén Argüero et al. They perform the first heart transplant in Mexico at the Specialty Hospital of the Medical Center "La Raza" of the Mexican Social Security Institute *(1, 5, 11)*. The 1-year survival rate for heart transplant recipients is close to 80-90% and is increasing every year and 5-year survival is 65% *(1, 2, 11)*. Heart transplanted patients are also exposed to trauma and accidents. The most common causes of trauma were car accidents and falls, which is why as anesthesiologists we must know the physiological and pharmacological problems of immunosuppression, the risks of infection, the potential for rejection and the behavior of these patients to anesthetic drugs (1.8). Transplanted patients are immunosuppressed and are more susceptible to the effects of soft tissue damage and poor bone healing. These patients should receive the same initial resuscitation as any trauma victim. And choosing the most appropriate anesthetic technique is a challenge, so it must be planned and analyzed before the surgical procedure minimizing hemodynamic changes. (2, 3, 4, 5)

II. Clinical Case

This is a 24-year-old male with a preoperative diagnosis of a bloody area in the left tibial region secondary to a bicycle fall in October 2018, which is programmed electively for taking and applying cutaneous auto grafting and allograft placement in the donor area. Which has the following important background; Post-operative cardiac transplant at 23 years due to heart failure and dilated cardiomyopathy secondary to vincristine, presenting after 15 days post-transplant acute pulmonary edema and pleural effusion so they put water seals on both sides, renal failure managed with hemodialysis from 23 years , at 6 months of extrauterine life, he presented leiomyosarcoma in his left shoulder without complications, which on the day of his pre-anesthetic evaluation used the following drugs: Sirolimus 1 mg per day. Mycophenolic acid 1 tablet every 12 hrs, spironolactone 25 mg every 12 hrs, furosemide 40 mg every 24 hrs, propanolol 20 mg every 12 hrs, pravastatin 10 mg every 24 hrs, omeprazole 40 mg every 24 hrs and prednisone 5 mg orally every 24 hrs. With Cushing syndrome fascie, weight 62 Kg Height: 158 cm with the following laboratory report hemoglobin 12.6 mg / dl, hematocrit 41% platelets 233000, leukocytes 6100, Glucose 80 mg / dl, creatinine 0.8 mg / dl, Prothrombin time 14 sec Thromboplastin time 31.9 sec, fibrinogen 511mg / dl Na 140 meq K 3.6 meq. Electrocardiogram: Sinus rhythm Heart rate 100 per minute with mild hypertrophy of the right ventricle,

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no arrhythmias, no ST elevation, absence of q waves, no ventricular extrasystoles. Echocardiogram: Preserved systolic function, 70% ejection fraction, no data on right ventricular dysfunction or pericardial effusion. Sirolimus levels of 12.4 ng / ml. Cardiac catheterization without pulmonary hypertension and with coronary arteries without obstructive lesions.

Patient is admitted to the operating room after authorization of informed consent is monitored, Blood Pressure 130-80 mmHg, Heart Rate 103 per minute, Respiratory Rate 18-22 breaths per minute, O2 Saturation 96-97%. Ondasetron 4 mg is administered intravenously, sedation with midazolam 2 mg intravenously, fentanyl 65 mcg intravenously, Oxygen is placed through nasal tips 3 liters per min, aseptic and antisepsis of the inguinal region is performed, subsequently scanned with Sonosite Edge II ultrasound with transducer linear 13-6 Hz with stimuplex for neurostimulation with 0.3-0.5 mA 0.3 ms 2 Hz, same region is located femoral artery and vein with pulsed doppler and doppler, femoral nerve is identified, skin is infiltrated with 2 cc of 1% lidocaine, 50 mm echogenic needle is inserted in the plane reaching the femoral nerve sheath and 20 ml of 2% ropivacaine is administered for surgical anesthesia, without presenting transanesthesia complications, latency 7 minutes satisfactory analgesia, cleaning and debridement of bloody area and taking of skin graft of left thigh approximately 5 cm and placed graft in bloody area of left tibia, as well as placement of aloinjerto of cultured skin (EPIFAST) in donor area.

No changes in hemodynamic parameters were observed after the administration of sedation, or after the administration of local anesthetic, buprenorphine was administered 130 mcg intravenously for postoperative analgesia, see *Fig. 1.* During his recovery stay he did not present significant changes in hemodynamic parameters, neither nausea nor vomit. Analgesia in the manipulated region was maintained for 6 hrs.

PARAMETERS	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Heart Frecuency	103 for min	103 for min	101 for min	101 for min	102 for min	101 for min
Breath Frecuency	19 for min	20 for min	22 for min	21 for min	21 for min	22 for min
Aretial Presion	130-80 mmHg	130-85 mmHg	130-85 mmHg	130-85 mmHg	130-80 mmHg	130-80 mmHg
O2 Saturatión	97%	97%	96%	96%	96%	96%
EVA	0	0	0	2	3	3

Figure 1: Hemodinamics parameters



Figure 2: Technique for performing ultrasound-guided femoral nerve block in the left inguinal region.

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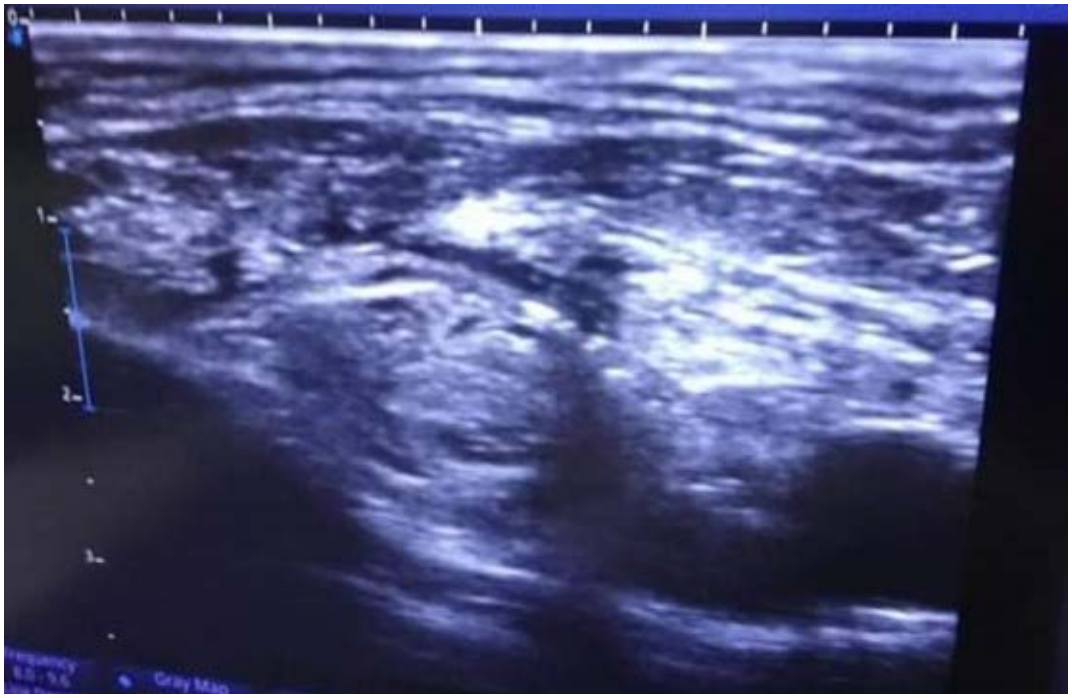


Figure 3: Econoanatomic image of the femoral nerve of the left inguinal region, observing femoral artery and femoral nerve resting on the iliopsoas muscle

III. Discussion

Patients with advanced HF before transplantation show different degrees of systolic or diastolic dysfunction (or both). The first leads to a decrease in ejection fraction and cardiac output, the second results in higher filling pressures. The reduction in cardiac output results in a reduction in the supply of blood, oxygen and nutrients to the terminal organs, which is only aggravated by partial venous congestion. After the cardiac output improves, and perfusion of the final organ is largely restored. But the transplant does not completely restore the patient to a non-pathological state. (1, 3.4)

The heart in normal conditions is innervated by sympathetic and parasympathetic fibers of the autonomic nervous system. And the sympathetic innervations towards the heart comes from the cervical ganglia and the upper thoracic sympathetic chain (T1-T4), the branches of the vagus nerves contribute to parasympathetic entry. The cardiac plexus, containing the sympathetic parasympathetic and postganglionic preganglionic fibers, is found at the base of the heart. The autonomic nervous system is the conduit through which it provides a supply of visceral sensory fibers to the pericardium (1, 3, 9).

During the transplant, the postganglionic neural axons that innervate the heart are transected, which is why it is considered a denervated heart. The cardiac reserves of norepinephrine are depleted and the autonomous influence on the heart ceases. This includes the response to baroreceptors. Afferent denervation prevents vasoregulatory responses by means of the renin-angiotensin axis, and the perception of pain secondary to ischemia (angina) is lost. (4,5) That is why we chose a nerve block for our patient to avoid as much as possible hemodynamic changes that could cause decreased cardiac output.

Coronary allograft vasculopathy (CAV) has been an important impediment to the long-term survival of heart transplant recipients, and one third of the patients developed atrio-ventricular communication after 5 years. Atrioventricular arrhythmias are rare but ectopic. Extrasystoles are common. The presence of arrhythmias generally indicates a severe acute rejection of coronary heart disease allograft (4,5) In the case of our patient, he entered with a sinus rhythm which he maintained throughout the perioperative period.

Regional anesthesia in this group of patients represents risks (epidural or spinal technique), since coagulation studies and platelet count should be normal. Patients taking azathioprine or antithymocyte globulin (ATG) may have thrombocytopenia, which increases the risks associated with central neural block. In neuroaxial blockade, the appropriate level of blockage should be taken into account, since a level of blockage that is too high can inhibit sympathetic nerves and cause vasodilation that is unfavorable for a transplanted heart; a very low level is not suitable for surgery since the resulting pain may cause an increase in myocardial oxygen consumption. (1,5) Azathioprine withdrawal in the perioperative period in patients taking warfarin may precipitate bleeding, since bleeding 6-mercaptopurine, the immediate metabolite of azthioprine, induces liver microenzymes that metabolize warfarin. Local anesthetics such as bupivacaine can

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have cardiotoxic effects at a conventional dose in these patients if they also have impaired renal function. (1) By choosing a nerve block for our patient, we minimize the risk of complications due to coagulation disorders, although were not present in the same should be avoided, using ropivacaine further reduces the risk of cardiac arrhythmias.

Peripheral nerve block has taken great importance in recent years and with the advances in technology such as the use of ultrasound to guide them have increased the safety and complications of both neuroaxial anesthesia and general anesthesia, nerve block Ultrasound guided femoral, taking the femoral artery and vein as a reference, the transducer is placed transversely on the anterior aspect of the anterior thigh below the inguinal ligament see *Fig 2,* on the femoral artery identifying the femoral artery, femoral vein, the iliac muscle, fascia lata, iliac fascia, and Sartorius muscle. The femoral nerve is below the iliac fascia at the angle between the iliac muscle and the femoral artery, see *Fig3,* flat techniques are preferred to visualize the path of the needle and it has been used successfully in hip and surgery. Knee for post-surgical analgesia since it grants post-surgical analgesia on the anterior thigh and knee (12, 13). That is why we decided to implement it in the management of skin loss lesions in reconstructive plastic surgery.

When a general anesthesia is chosen, it should be taken into account that the transplanted heart does not have sympathetic, parasympathetic or sensory innervation since it was lost in the transplant surgery, and the loss of vagal influence causes a resting heart rate higher than normal (91-101 bpm). Two P waves can be observed so there is a P: 1 that represents the SA of the recipient node and the other one that represents the donor SA node. Although the innate pacemaker remains intact from the original heart, its electrical activity cannot be conducted through the suture line. (1,3)

Intrinsic mechanisms and coronary self-regulation remain intact, carotid sinus massage and Valsalva maneuver have no effect on heart rate, there is loss of cardiac barreflexes and loss of sympathetic response to laryngoscopy and tracheal intubation. The denervated heart may have a more dull heart rate response at an anesthetic depth or inadequate analgesia. In the denervated heart, the response of catecholamines is different from that of the normal heart because intact sympathetic nerves are required for the normal uptake and metabolism of catecholamines. The transplanted heart may respond to direct-acting drugs (eg, sympathomimetics) (5, 10, 11).

Epinephrine and norepinephrine have an increased inotropic effect on heart transplant recipients. Both have a greater proportion of β to α or inotropic to vasoconstrictor. Dopamine acts by the release of norepinephrine and is a less effective inotropic in the denervated heart (1, 4, 5). Isoproterenol and dobutamine have similar effects on denervated and normal hearts. Therefore, both are effective inotropics in the denervated heart and are frequently used Ephedrine, has reduced responses on blood pressure and heart rate. There is still a response of venous contrition reflects hypotension. Therefore, intravascular volume is even more important. Circulating catecholamines cause a delayed increase in rate and contractility (5). The Frank-Starling mechanism remains operative in the transplanted heart (4, 10,11) Patients with a transplanted heart are "dependent on preload." (3) These patients are at high risk of presenting atrial flutter or fibrillation in a few years, this is due to the onset of reinnervation, complete neuronal control is achieved after 15 years of transplantation (5) First degree atrioventricular block is frequent, and up to 30% have a right branch block (4)

Vagolytics, such as atropine, are ineffective in increasing heart rate, other positive chronotropic medications, such as ephedrine and isoproterenol. Inhaled anesthetics have myocardial depressing properties, they are well tolerated unless there is significant heart failure, dopamine is an ineffective inotropic. Epinephrine / norepinephrine may have exaggerated beta-mimetic effects on heart rate because the increase in blood pressure will not lead to a decrease in heart rate through the baroreceptor reflex (i.e., the efferent vagus nerve). Implanted mechanical pacemakers normally work in heart transplant recipients since the heart cables are placed directly in the myocardium (2, 3, 4,5). In the case presented, there was no need to use any vasoactive drug since the patient had hemodynamic stability.

Transesophageal echocardiography has a very important role prior to surgery, invasive hemodynamic monitoring in heart transplant recipients is performed according to the type of surgery and the hemodynamic state of the patient (3, 4,5) Some authors prefer general anesthesia, since there is the possibility of an altered response to hypotension after spinal or epidural anesthesia. In our patient we chose a safer technique that was ultrasound-guided neurostimulation-guided femoral nerve block to maintain surgical anesthesia and optimal postoperative analgesia.

Preoperative evaluation is of great importance to determine the safest anesthetic application to the post-transplant patient. Professionals should focus the evaluation on the current function of the heart taking into account the level of exercise tolerance, evaluation of the transesophageal echocardiogram and stress test results, and / or should request a cardiology assessment. An echocardiography should be performed to detect Vasculopathy that is common in patients more than 1 year after transplantation and is the most frequent cause of repeated transplantation or death after 1 year (4, 5,6). Close communication must be made between the surgeon and the anesthesiologist, to detect preoperative arrhythmias that occur in 5% of patients,

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complete blood count, renal function tests, liver function tests, serum electrolytes as well as coagulation tests. Cyclosporine should be administered 4-7 days prior to surgery to maintain therapeutic levels. As well as the administration of prednisone or methylprednisolone (1, 4,5)

Patients with heart transplants often receive corticosteroid therapy, it is important to provide more glucocorticoids to those patients who present with chronic corticosteroid use (5 mg / day of prednisone or equivalent). (one)

IV. Immunosuppressors to Avoid Rejection

The immunosuppressive drugs available today can be classified into:

Inductors:

OKT3, thymoglobulins and antagonists of IL-2 receptors (daclizumab and basiliximab). Anticalcineurinics:

Cyclosporine and tactrolimus.

Antimetabolites or purine synthesis inhibitors:

Mycophenolate mofetil and azathioprine.

Corticosteroids

Antiproliferatives

Sirolimus and everolimus.

These drugs can be combined in various ways, constituting immunosuppression guidelines, which can be classified according to their indication: induction, maintenance and rejection. r purpose to block the immune response in the initial period of transplantation (when it is more intense), but with the cost of a higher incidence of infections and neoplasms. (14) In the case of our patient he was being treated with sirolimus and steroids.

V. Transanesthetic

The objective of surgical intra-management of patients with heart transplants who undergo non-cardiac surgery is to avoid hypotension, vasodilation and acute decrease in preload due to the importance of diastolic volume to maintain cardiac output (8). Standard monitoring is indicated and varies according to the type of surgery, anesthesia technique and the patient's condition. Invasive CVP and arterial monitoring were not used in this case due to the patient's preoperative period as it was thermodynamically stable, the surgical risk was minimal in this case given the anesthetic management that was performed (3,4,8).

Side effects of immunosuppressive medications, which could have an impact on the management of anesthesia. The use of medications that produce active metabolites such as morphine, meperidine and non-depolarizing muscle relaxants should be prevented. Any anesthetic that inhibits or induces CYP-450 can affect the plasma concentration of tacrolimus. Barbiturates induce CYP-450, therefore lowering the blood level of tacrolimus. Propofol inhibits CYP-450, respiratory failure has been observed in approximately one third of patients with the administration of tacrolimus and propofol (4, 5, 6, 7) Cyclosporine has shown a similar behavior with barbiturates, fentanyl and isoflurane. Infectious complications are an important cause of morbidity and mortality; the causative agents associated were bacteria (43.6%), viruses (41.7%), fungi (10.2%), P pneumocystis carinii (4%) and protozoa (0.6%). (3) Oral to nasal intubation is preferred since there is a risk of infection with the latter caused by nasal flora. Airway obstruction may occur in patients with lymphoproliferative processes and diabetes (5), such as In the case of our patient who presented leiomyosarcoma in the left shoulder, cyclosporine can lead to gingival hyperplasia and cause bleeding (4), non-steroidal anti-inflammatory drugs should be avoided to control pain due to the risk of bleeding, so in our patient we use opioids for its management. (5)

The dose of benzodiazepines should be reduced when the patient consumes immunosuppressants as they increase their potency. Atracurium and cisatracurium are preferred since these are safer in patients with liver and kidney disorders. Neostigmine generally has no effect on heart transplantation. But precautions should be taken when reinnervation begins (> 1 year post-transplant) because there is evidence of bradycardia and cardiac arrest with neostigmine despite the concurrent use of an antimuscarinic agent. Cyclosporic increases the analgesic effect of fentanyl (4.5.6).

In the case of our patient, the presence of clinical signs of Sepsis such as elevated temperature, elevated white blood cells, cell count and the presence of chills was monitored.

VI. Postoperative Care

Preload status, renal function and infection prevention should be monitored. Immunosuppressants should be continued after the operation and the blood level should be monitored. In the case of our patient, the healing was followed by accelerating it in the donor area with the application of cutaneous allograft which was removed after 5 days presenting complete re-capitalization and without presenting infection data. And the integration of the skin graft in the traumatized area was observed at 7 days (5, 7.9).

VII. Conclusions

The anesthesiologist should have a solid knowledge about the newly established functions of a transplanted heart, its specific perioperative care considerations and the pharmacological effects of

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immunosuppressive medications, the importance of preload dependence; administering direct vasoactive drugs if necessary; and awareness of the infectious risk, potential for rejection, and the possible side effects of an immunosuppressive regimen are very important to prevent perioperative complications (5,14). So the success of the anesthetic surgical procedure is due to the maintenance of the preload, the sinus rhythm and afterload. (4,8) In the clinical case, we present a safer and more effective alternative for the management of traumatic injuries in reconstructive plastic surgery without significant changes in hemodynamic parameters and with adequate postoperative analgesia and without perianesthetic complications (12,13)

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Changes in Physical Qualities and Quality of Life after a Physical Conditioning Program in Hemodialysis Patients at the San José Renal Unit, Bogotá

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Resumen- *Introducción:* La enfermedad renal crónica es definida como perdida progresiva e irreversible de la función renal, asi mismo cambios en la cualidades físicas, bioquímicas y calidad de vida de las personas en diálisis.

Objetivo: Evaluar cambios en las cualidades físicas, bioquímicas y calidad de vida después de un programa de acondicionamiento físico en pacientes en hemodiálisis de la unidad renal San José, Bogotá.

Metodología: Esta es una entrega preliminar de la primera parte de la muestra de un estudio cuasi experimental, donde participaron pacientes del programa de Hemodiálisis la Unidad Renal del Hospital de San José – Fresenius Medical Care ®.

Palabras Clave: *insuficiencia renal crónica, diálisis renal, calidad de vida, ejercicio.*

GJMR-F Classification: *NLMC Code: WB 460*

CHANGESINPHYSICALQUALITIESANDQUALITYOFLIFEAFTERAPHYSICALCONDITIONINGPROGRAMINHEMODIALYSISPATIENTSATTHESANJOSERENAL UNITBOGOTA

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Changes in Physical Qualities and Quality of Life after a Physical Conditioning Program in Hemodialysis Patients at the San José Renal Unit, Bogotá

Cambios En Las Cualidades Físicas Y Calidad De Vida Después De Un Programa De Acondicionamiento Físico En Pacientes En Hemodiálisis De La Unidad Renal San José, Bogotá

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Resumen- Introducción: La enfermedad renal crónica es definida como perdida progresiva e irreversible de la función renal, asi mismo cambios en la cualidades físicas, bioquímicas y calidad de vida de las personas en diálisis.

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Resultados: Se incluyeron 17 sujetos con una media de edad de 64 ± 14,8, años, se encontró mejoría en el puntaje general de la escala SF36 con un valor de p <0.05, a favor de la rutina, cambio en el nivel de fuerza a favor aunque no significativo (p= 0.08).

Conclusiones: Aunque es una entrega parcial se aprecia una cambio a favor en las pacientes con diálisis, se hace necesaria la continuación del estudio aumentando el tamaño de la muestra y por lo tanto las diferencias.

Palabras Clave: insuficiencia renal crónica, diálisis renal, calidad de vida, ejercicio.

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I. Introducción

La enfermedad renal crónica (ERC) se define como una pérdida progresiva e irreversible de la función renal asociado a deterioro de la tasa de filtración glomerular, secundaria a diferentes patologías: hipertensión arterial, diabetes mellitus, lupus eritematoso sistémico, entre otras(1). Esta entidad tiene una importante prevalencia a nivel mundial, con todas las repercusiones que ello conlleva en costos de salud y calidad de vida de los pacientes. El Sistema de Datos Renales de EE. UU. (US Renal Data System - USRDS) en su informe anual de 2019, reporto que para el 2017 se presentaron 124.500 casos nuevos de enfermedad renal terminal, con una tasa de incidencia bruta de 370,2 por millón/ año, de los cuales el 86,9% recibieron tratamiento con hemodiálisis, el 10,1% con diálisis peritoneal y el 2,9% trasplante renal. Además, una prevalencia de 2.204 por millón en la población de EE. UU, siendo los hombres y la población de raza negra los de mayor prevalencia. (2)

En Colombia, para el año 2015, la prevalencia de ERC fue de 66,8 por cada 100.000 habitantes, siendo más alta en hombres (78,4 por cada 100.000 habitantes) que en mujeres (57,3 por cada 100.000 habitantes). Se identificaron 34.469 personas con terapia de reemplazo renal calculándose una prevalencia de 71,5 por 100.000 habitantes. Para el año 2007 la prevalencia era cercana a 530 pacientes por millón, con una tasa de incidencia calculada de 140 pacientes por millón (3) y según el reporte del 2015 de la CAC la prevalencia general de ERC 5 en el país ha aumentado progresivamente. El estudio Enríquez et al para Colombia reportan una sobrevida a 5 años del 54% y a 10 años del 57% una vez inician un programa de hemodiálisis(4).

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En los pacientes con ERC existen factores como la debilidad muscular y la mala tolerancia al ejercicio que llevan a la inactividad y sedentarismo(5); Padilla et al demostraron que el rendimiento físico medido por el consumo máximo de oxígeno (VO2 pico), la prueba de caminata de 6 minutos, la velocidad máxima de la marcha y la prueba de sentarse y pararse, es menor a los valores estándar para población sedentario(6). Además, aquellos que están en hemodiálisis son entre 20 y 50% menos activos que las personas sedentarias sanas (7, 8). Sin embargo, documentos como el Estudio de Morbilidad y Mortalidad en Diálisis (Dialysis Morbidity and Mortality Study - DMMS) y las pautas de práctica clínica K / DOQI para enfermedades cardiovasculares en pacientes en diálisis, entre otros recomiendan la actividad física en estos pacientes (9, 10) con el objetivo de mejorar su capacidad funcional, calidad de vida y disminuir los riesgos asociados al sedentarismo.

Segura-Ortí, a través de su revisión sistemática mostró la seguridad de los programas de ejercicio durante la HD y los efectos positivos sobre la capacidad aeróbica, la capacidad física funcional, la fuerza y la calidad de vida(11). Sin embargo los beneficios de estos programas de actividad física se ofrecen en la minoría de unidades renales en el mundo. También se han demostrado resultados favorable al reducir la Tensión Arterial Sistólica (TAS) y Diastólica (TAD), al igual que en los valores del perfil lipídico pues se ha asociado a disminución de triglicéridos y elevación del colesterol HDL (12, 13).

Toussaint y cols. demostró que un programa de ejercicio en cicloergómetro de 3 meses de duración en HD, redujo el péptido natriurético cerebral, lo cual significa una reducción del riesgo cardiovascular (RCV)(14). También se ha demostrado que los pacientes en HD que han presentado un evento cardiovascular y participan de un programa de rehabilitación cardiaca, presentan una reducción del 35% de todas las causas de mortalidad y 36% del riesgo de morir por un evento cardiaco comparado con aquellos en HD que no recibieron rehabilitación cardiaca (13, 15).

Las guías para los pacientes con nefropatía crónica recomiendan programas con frecuencias de 3 a 5 días por semana en ejercicio aeróbico y 2 a 3 días por semana en ejercicio de fuerza; con una intensidad moderada en el ejercicio aeróbico (IEPíndice de esfuerzo percibido de 11-13/20) y en el de fuerza entre el 60 al 75% de 1 repetición máxima (RM); de 20 a 60 minutos ejercicio aeróbico al día, continuo o intermitente y se sugiere caminar y montar en bicicleta. En el entrenamiento de fuerza 1 serie de 10 a 15 repeticiones según tolerancia del paciente, y se indica el uso de máquinas o peso libre con ejercicios isotónicos e isométricos (5, 16). Se recomienda además en pacientes con hemodiálisis realizar el ejercicio durante la primera mitad del tratamiento para evitar la hipotensión (8, 11), como indicador se usa una escala de percepción del esfuerzo, pues la frecuencia cardiaca es poco fiable y además se puede ejercitar el brazo donde está el acceso arteriovenoso (AV) siempre y cuando no se apoye peso directamente en esa área(5). Sin embargo, a pesar de toda la evidencia, la prescripción ideal no se ha concretado del todo en pacientes con esta patología.

Pero aunque la literatura destaca los beneficios del ejercicio durante la hemodiálisis, los protocolos de intervención son variados; además en Colombia no hay studios con este tipo de intervención. Por lo cual, se planteó la realización de este studio con el objetivo de implementar un plan de ejercicio intradialisis con los pacientes de la unidad renal del Hospital San José-Fresenius Medical Care ® y evaluar los cambios en las cualidades físicas, bioquímicas y calidad de vida antes y después del mismo; además de proporcionar información de la seguridad de esta intervención y proponer un modelo de intervención y así lograr una herramienta con validez interna.

II. Métodos

Se llevo a cabo un estudio cuasiexperimental de antes y después, con una muestra parcial de 17 sujetos los cuales fueron reclutados del programa de Hemodiálisis la Unidad Renal del Hospital de San José - Fresenius Medical Care ®. Cada paciente dio su consentimiento informado; el protocolo fue aprobado por el Comité de Ética del Hospital San José de Bogotá. Dentro de los criterios de inclusión para el studio se tuvieron en cuenta pacientes mayores de 18 años, que hubiesen ingresado a hemodiálisis en un periodo superior a 6 meses y que asistieron por lo menos 3 veces por semana. Se excluyeron aquellos con antecedentes de enfermedad coronaria aguda, hipertensión pulmonar severa, anemia severa igual o menor a 6 g/dl de hb, amputación o patologías neuromusculares que impidieran la realización de ejercicio, problemas psiquiátricos o cognitivos, presencia de enfermedad aguda que lo incapacite para realizar 4 o más sesiones continuas, paciente con neoplasias asociadas, con fístula AV en miembros inferiores, que se encuentre participando en otros estudios o pacientes con clasificación de riesgo cardiovascular AHA C y D.

Se incluyeron en este primer reporte una muestra de 17 pacientes del total de 32 que están establecidos como tamaño total de la muestra. Para evaluar los desenlaces se aplicó el Test SF-36, realización de test de caminata de 6 minuto, medición de la fuerza mediante prensión de la mano bilateral (hand grip) con un dinamómetro Marca LITE® 200 LB y toma de Kt/V un parámetro calculado de forma automática por la maquina dializadora. La intervención

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se llevó a cabo durante 12 semanas, 3 sesiones por semana, en las primeras 2 horas de la diálisis. Se inició con 5 minutos de calentamiento con movilidad articular (1 serie de 10 repeticiones por cada articulación de forma bilateral), seguido de 20 minutos de ejercicio cardiovascular en cicloergómetro marca CHATTANOOGA® con una intensidad de 3 a 5/10 según escala BORG modificada. Se continuo con 20 minutos de trabajo de fuerza con bandas elásticas al 40% de 1RM (Repetición máxima), realizando ejercicios de extremidades inferiores y de la extremidad superior libre (flexo extensión y/o abducción aducción y/o ejercicios compuestos contra resistencia con las bandas elásticas-roja o verde). La progresión se realizó en volumen y carga del 5 al 10% de 1RM cada mes según tolerancia. Se sesión finalizo con 5 minutos de recuperación.

Las sesiones de ejercicio fueron dirigidas y monitorizadas por médicos residentes de Medicina de la Actividad Física y del Deporte. En cada sesión se monitorizaron los parámetros de frecuencia cardiaca (FC), tensión arterial (TA) y el índice de esfuerzo percibido con la escala de Borg modificada; además se evaluó la presencia de síntomas (angina, mareo, síncope, disnea) y signos de alarma (tensión sistólica igual o mayor a 200 mmHg y/o diastólica mayor o igual a 110 mmHg, o la disminución durante la sesión de por lo menos 20mmHg de la TA sistólica respecto a la basal), que pudieran llevar a la suspensión de la sesión. Los datos recolectados por los médicos a cargo de la sesión, fueron consignados en medio físico y posteriormente digitalizados en una base de datos en Microsoft Excel®.

Se consideraron perdidas para el seguimiento y no se tuvieron en cuenta para el análisis estadístico, todos aquellos pacientes que presentaron alguna enfermedad infecciosa aguda, hospitalización, traslado a otra unidad renal, cambio de estrategia de tratamiento -diálisis peritoneal, trasplante- o muerte, que les impidió asistir a 4 o más sesiones continúas; o aquellos que al finalizar el programa tuvieron un cumplimiento menor de 75% de la totalidad de las sesiones programadas. Con el animo de encontrar diferencias entre el inicio y la medición final se llevó a cabo pruebas no paramétricas por medio de la prueba de T para muestras relacionadas con un nivel de significancia del 95%

III. Resultados

Se incluyeron en esta primera parte un total de 17 sujetos en la investigación, con una edad mínima de 19 años y una máxima 80 años con una media de 64.4±14.8 años, 13 de ellos correspondía a genero masculino representando el 76% de la muestra.

Al iniciar se llevo a cabo la realización de la medición por medio de la escala SF36 a todos los sujetos encontrando un puntaje promedio del grupo de 52.8±24, del total de ingresados al estudio el 55,6% presentaron un puntaje SF36 menor de 50 al inicio, mostrando un peor estado de salud al inicio de la investigación, con relación al puntaje final de la escala SF36 donde solamente el 27,8% mostraron un puntaje desfavorable, se encontró una diferencia de 12.47 entre en antes y el después, siendo esta diferencia estadísticamente significativa (valor p 0.005), mostrando mejora en el puntaje posterior a la intervención de ejercicio. (Tabla 1)

Tabla No 1: Caracteristicas descriptivas

	N	Mínimo	Máximo	Media	Desv. típ.
Edad	17	19,00	80,00	64,3529	14,82372
puntaje SF36 inicial	17	23,00	100,00	52,8824	24,19939
caminata Inicial	18	76,00	259,00	162,6111	46,43166
medicion fuerza mano dereche inicial	17	6,00	60,00	24,4706	10,79420
medicion fuerza mano izquierda inicial	17	10,00	61,00	23,8824	12,33837
Puntaje SF36 Final	17	34,00	95,00	65,3529	18,47614
Caminata final	17	91,00	220,00	170,4706	32,63648
medicion fuerza mano derecha final	17	3,00	34,00	26,0588	7,19783
medicion fuerza mano izquierda final	17	18,00	34,00	24,6471	4,72944
N válido (según lista)	16				

Al inicio de la investigación se tomaron los valores de la fuerza mediante prensión de la mano (hand grip), siendo este un indicador de fuerza global, los valores se tomaron tanto en mano derecha como en izquierda, los valores iníciales se contrastaron con los valores finales, con el ánimo de observar un cambio en el nivel de fuerza, se encontró como al momento de la inclusión en mano derecha el valor medio fue de 24,47 ± 10,79 Kg; para mano izquierda 23,8 ± 12,33 Kg, al finalizar la intervención se encontró 26,06 ± 7,19 Kg y 24,6±4,72 Kg para manos derecha e izquierda respectivamente mostrando una diferencia en el valor de puntaje inicial con relación al final no siendo sin embargo este cambio estadísticamente significativo (p 0.433 para mano derecha y 0.738 para mano izquierda).

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La relación entre caminata inicial y final que también fue evaluada en el estudio, con el ánimo de comprobar prueba de resistencia al ejercicio aeróbico con el test de caminata de 6 minutos se encontró una media inicial de caminata 162 ± 46,43 y al final el resultado obtenido fue de 170 ± 32,6, mostrando una mejoría en el valor medio de resistencia en el 72,2% de los participantes al estudio, sin embargo, esta mejoría en el valor medio no fue estadísticamente significativo con un valor de p de 0,07.

IV. Discusión

Luego de llevar a cabo este estudio preliminar, se encontró que aunque el tamaño de la muestra es limitado (17 participantes), se deseó llevar a cabo este análisis parcial, donde encontramos que aunque no es significativa estadísticamente la diferencia entre las mediciones iniciales y las finales (por el tamaño de muestra) se pueden apreciar cambios en los valores de las escalas evaluadas, la necesidad de continuar con la investigación se da en la medida que al aumentar el tamaño de muestra se podrá encontrar mayores diferencias a favor de ejercicio en pacientes con diálisis.

Un punto que arrojo una diferencia estadísticamente significativa y que amerita un mayor esfuerzo es el relacionado con la medición de la escala SF36, la cual nos muestra una mejora en la condición física de los pacientes con diálisis que llevaron a cabo la rutina de ejercicio, está mejoría es concordante con la obtenida por Stavroula Ouzouni y colaboradores quienes encontraron que la mejora en la calidad de vida dependía de la participación en programas de ejercicio, los efectos del entrenamiento y la reducción del nivel de depresión fueron notables en este grupo de pacientes(17), lo cual se relaciona con los resultados preliminares obtenidos en nuestra investigación.

En los resultados del test de caminata de 6 minutos aunque se presentó una mejora en los metros recorridos, debido al pequeño tamaño de muestra no fue significativa pero fue concordante con lo encontrado por Parsons y colaboradores los cuales mostraron un aumento del 14%(18), y los resultados de Kirsten P. Koh quienes no demostraron una mejoría luego de una rutina de seis meses(19), mientras que en los resultados parciales del presente estudio fue de 5% de mejoría, lo cual indica la necesidad de continuar con un tamaño de muestra mayor, lo cual lleva a concluir que aunque se presenta una discrepancia en resultados en la literatura nuestro studio apunta a la mejoría de la resistencia en nuestro pacientes de diálisis.

Aunque nuestro estudio por las limitación de tamaño de muestra y por tratarse el presente artículo una entrega parcial, mostro una mejoría en la fuerza muscular en los pacientes sometido a ejercicio lo cual es concordante con los estudios de Chemma y colaborados lo mismo que los de Vicent Esteve y colaboradores (20,21).

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Declaración De Conflicto De Interes

Los investigadores declaramos no tener conflictos de interés.

Declaración De Financiacion Del Proyecto

Los autores declara que para la realización de este estudio se recibió financiación por parte de la Fundación Universitaria de Ciencias de la Salud FUCS, para la adquisión de los implementos para la ejecución de los ejercicios.

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Complex sSMC Involving X and Y Chromosomes in two Patients with 45,X/46,X,+mar Karyotype

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Abstract- Complex small supernumerary marker chromosomes (sSMCs) consist of chromosomal material derived from two or more different chromosomal regions and constitute one of the smallest subsets of sSMC. Most of complex sSMCs are represented by a der(22)t(11;22) in Emanuel syndrome. As far as we know, only one recent report has described sSMCs involving simultaneously X and Y chromosomes in Turner Syndrome.

We report two patients, a female and a male, both with a complex sSMC derived from X and Y chromosomes in mosaic with a 45,X cell line. In both patients, the marker chromosomes were early replicating and the *XIST* gene was absent. FISH and PCR confirmed the presence of Yp loci (*TSPY, AMGY, SRY,* DYZ3), and negative for DYZ1. The DAZ4 sequence was present only in patient 1. Our findings suggested that complex sSMC involving X and Y chromosome could be a kind of sSMC of the gonosomes.

Keywords: molecular cytogenetics, mosaicism. sex chromosomes, complex small supernumerary marker chromosome, turner syndrome.

GJMR-F Classification: NLMC Code: QS 677



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Complex sSMC Involving X and Y Chromosomes in two Patients with 45,X/46,X,+mar Karyotype

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Abstract- **Complex small supernumerary marker chromosomes (sSMCs) consist of chromosomal material derived from two or more different chromosomal regions and constitute one of the smallest subsets of sSMC. Most of complex sSMCs are represented by a der(22)t(11;22) in Emanuel syndrome. As far as we know, only one recent report has described sSMCs involving simultaneously X and Y chromosomes in Turner Syndrome.**

We report two patients, a female and a male, both with a complex sSMC derived from X and Y chromosomes in mosaic with a 45,X cell line. In both patients, the marker chromosomes were early replicating and the *XIST* gene was absent. FISH and PCR confirmed the presence of Yp loci (*TSPY, AMGY, SRY,* DYZ3), and negative for DYZ1. The DAZ4 sequence was present only in patient 1. Our findings suggested that complex sSMC involving X and Y chromosome could be a kind of sSMC of the gonosomes.

Keywords: molecular cytogenetics, mosaicism. sex chromosomes, complex small supernumerary marker chromosome, turner syndrome.

I. Introduction/background

Complex small supernumerary marker chromosome (sSMC) consist of chromosomal material derived from two or more different chromosomal regions (Liehr, 2012). sSMC are only identifiable by molecular cytogenetic analysis, because their size and the variability of involved chromosomal regions (Trifonov *et al*., 2008). The characterization of the structure, regions and genes involved in the sSMC are important for the genotype-phenotype correlation (Liehr, 2012).

Complex sSMC constitute 8.4% of all sSMC, and are observed mainly in Emanuel syndrome (ES; 82.2%) (Liehr *et al*., 2013). Fewer than 100 cases are known (Liehr *et al*., 2013). Excluding ES cases, as they are difficult to identify and their frequency is underestimated (Trifonov *et al*., 2008; Liehr *et al*., 2013).

Parental studies in 57 complex sSMCs (excluding ES) showed that 36% of them were *de novo*, and the remainder (64%) were inherited from a balanced translocation in one parent. Mosaic cases with karyotype 47,XN,+mar/46,XN were only seen in *de novo* complex sSMCs (Liehr *et al*., 2013).

sSMC can be present in numerically abnormal karyotype like in a Turner syndrome (TS) karyotype (45,X/46,X,+mar), leading to female or male phenotypes (Liehr *et al*., 2007; Wang *et al*., 2017). In TS, the sSMC are derived from one of the gonosomes in more than 99% of the cases; there are also exceptional reports on sSMC derived from autosomes (Liehr *et al*., 2007; Wang *et al*., 2017; Sheth *et al*., 2009; Jafari-Ghahfarokhi *et al*., 2015).

Recently, a complex sSMC from X and Y chromosomes have been described in a Turner syndrome (Li *et al*, 2020). Here we report two mosaic patients, a TS patient and an unidentified syndrome male, with a 45,X cell line and a cell line with complex sSMC involving X and Y chromosomes, characterized by Fluorescence *in situ* hybridization (FISH) and Polymerase Chain Reaction (PCR).

II. Methods

Patient 1 (P1) come from a cohort of 21 TS patients with marker chromosomes, and Patient 2 (P2) from another cohort of 19 patients with uncharacterized marker chromosomes, evaluated in Cytogenetic Laboratory of IPPMG, UFRJ. The informed consent was obtained from the patients or their parents (Approved by the Ethics Committee of IPPMG/UFRJ nº 13/09).

Chromosomes were examined using G banding and differential replication staining (late BrdU labelling). Fluorescence *in situ* hybridization (FISH) were performed using commercial probes: Whole Chromosome Painting (wcp) X and Y, XYpter and XYqter, *SHOX* (Xp22 and Yp11.3), *KAL1* and *STS* (Xp22.3); *XIST* (Xq13.2), DYZ3 (Yp11.1-q11.1), *SRY*

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(Yp11.31) and DYZ1 (Yq12), according manufacturers' instructions.

Genomic DNA was isolated from peripheral blood using a commercial DNA isolation kit and the polymerase chain reaction (PCR) was performed using six primers sets for Y-chromosome-specific sequences: *SRY* (Yp11.31), *TSPY1* (Yp11.2), *AMGY* (Yp11.2), *DAZ4* (Yq11.23), DYZ3 (Yp10-q10) and DYZ1 (Yq12).

III. Clinical Informations

P1: female, referred at 7 years of age due to short stature. First child of an unrelated couple, a young mother and an unknown father. Vaginal delivered at 40th week gestation; birth weight of 2.6kg and birth length of 48cm. She developed short stature, developmental delay and intellectual disability. Menarche was induced at 17th year. On physical examination at 30th year she presented: short stature (145cm; not treated with growth hormone), relative macrocephaly, ocular hypertelorism, high-arched palate, short neck, low posterior hairline, shield shaped thorax, widely spaced nipples, cubitus valgus, multiple pigmented nevi, hyperconvex nails, hypoplasia of the second toe, bicuspid aortic valve and obesity (Fig. 1a) and a typically female external genitalia. Ultrasound examination showed reduced uterus and unidentified ovaries. Prophylactic gonadectomy was recommended.

P2: male, referred at 4 years of age due to neuropsicomotor developmental delay, autistic behaviour, aggressiveness and hyperactivity. First child of a healthy and unrelated young couple. Maternal thrombocytopenia. Vaginal delivered at 38th week gestation; birth weight of 2.3Kg, birth length of 47cm and head circumference of 32cm. He didn't walk until his 15th month of age. Speech delay was evident by 2 years of age. Recurrent episodes of pneumonia. On physical examination at 8 years, he presented triangular face, ocular hypertelorism, arched eyebrows, long eyelashes, long palpebral fissures, high-arched palate, diastema, widely spaced nipples, single transverse palmar crease (Fig. 1b) and a typically male external genitalia (normal scrotum, palpable testes and a normal sized penis). Ultrasound examination showed normal prostate size and absente Müllerian remnants. No specific syndrome could be related to this patient clinical symptoms.



Figure 1: Appearance of P1 and P2: a) P1: 30-years-old, woman showing minor facial dysmorphic features and hypoplasia of the second toe. b) P2: 8-years-old, boy phenotype showing minor facial dysmorphic features, ocular hypertelorism and bilateral transverse palmar crease.

P1: Karyotype was 45,X/46,X,+mar; the marker chromosome was a dicentric sSMC, with early replication, and alternating morphology. The mother presented normal karyotype.

The sSMC was positive for both X and Y with wcp, and presented two copies of XYpter, DYZ3, *SRY* and *SHOX*, one copy of *KAL1* and *STS*; was negative for *XIST*, DYZ1 and XYqter (Fig. 2). The wcp analysis also showed the presence of cryptic cell populations, one with the presence of an sSMC derived from chromosome X(wcpX+) and another with a sSMC derived from chromosome Y(wcpY+), but the frequency of these cells was too low to be determined. The frequency of nuclei with two DXZ1 signals was 1,7%. In each metaphase only one sSMC was observed.

PCR was positive for *TSPY1, AMGY, SRY,* DYZ3 and *DAZ4,* and negative for DYZ1.

The redefined karyotype was: mos 45,X/46,X,+mar.ish.der(X;Y)(DYZ3++,SHOX++,SRY++,KAL1+,XYpter++,wcpX+,wcpY+,XIST-,STS-, DXZ1-,DYZ1-)

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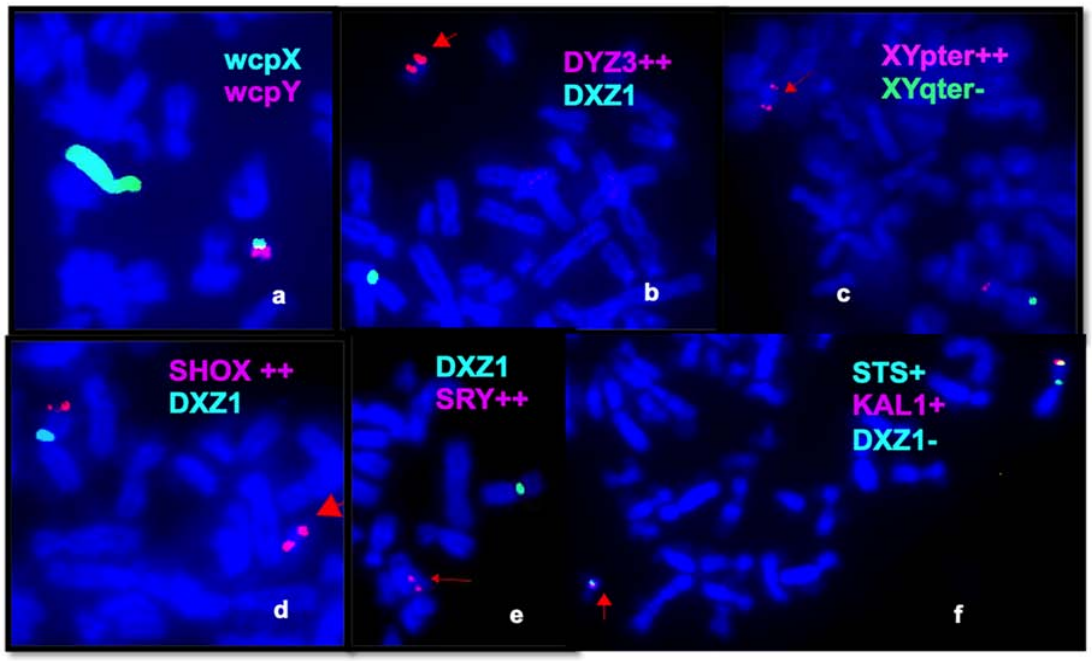


Figure 2: FISH results for P1. Partial metaphases showing the presence of: a) both signals of wcpX and wcpY (red arrow) indicating the participation of X and Y chromosomes in complex sSMC; b) two copies of DYZ3 (red arrow); c) two copies of XYpter (red arrow); d) two copies of SHOX (red arrow); e) two copies of SRY (red arrow) and f) one copy of STS/ KAL1 (red arrow).

P2: Karyotype was 45,X/46,X,+mar, the marker chromosome was a *de novo* ring sSMC, early replicating. Both parents presented normal karyotype.

The sSMC was positive simultaneously for X and Y with wcp, and presented one copy of XYpter, DYZ3, *SRY*, *SHOX*, and *KAL1*; it was negative for *XIST*, *STS*, DYZ1(Yq12) and XYqter (Fig. 3). Sometimes the sSMC appeared to be dicentric.

PCR was positive for *TSPY, AMGY*, *SRY*, DYZ3 and negative for DAZ4 and DYZ1.

The redefined karyotype was: mos 45,X/46,X,+mar.ish.der(X;Y)(DYZ3+,SHOX+,SRY+,KAL1+,XYpter+,wcpX+,wcpY+,XIST-,STS-,DXZ1-,DYZ1-)

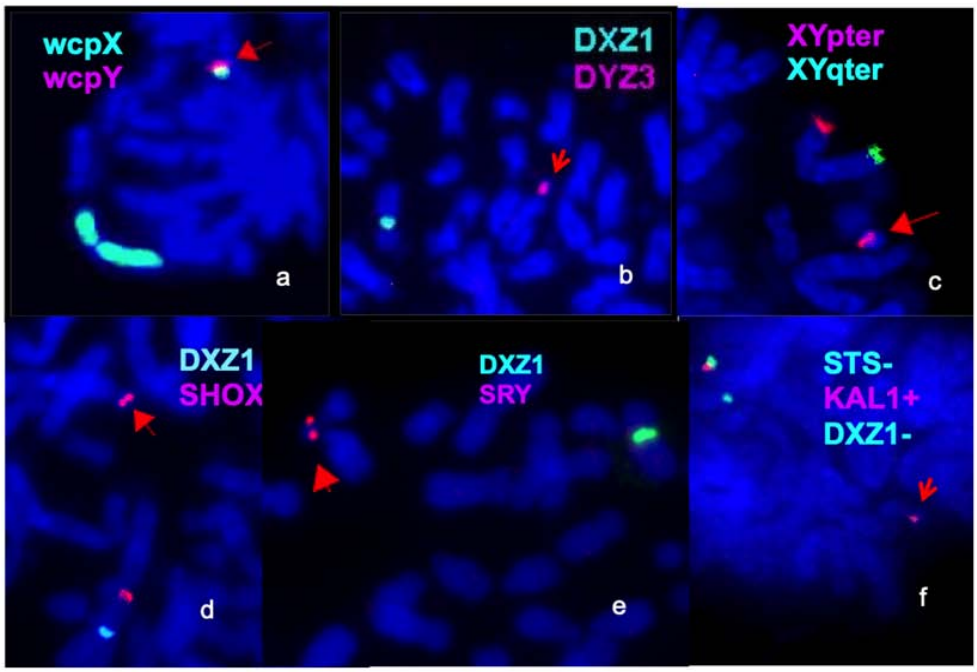


Figure 3: FISH results for P2. Partial metaphases showing the presence of: a) both signals of wcpX and wcpY (red arrow) indicating the participation of X and Y chromosomes in complex sSMC; b) DYZ3 (red arrow); c) XYpter (red arrow); d) SHOX (red arrow); e) SRY (red arrow) and f) KAL1(red arrow).

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IV. Discussion and Conclusion

We report two original cases of complex sSMC, a TS patient and a unidentified syndrome male patient involving X and Y chromosomes, both mosaic with a 45,X cell line. Molecular techniques were crucial to determine the presence of the Y chromosome material in these patients. The presence of Y chromosome segments could increase the risk for gonadoblastoma. Prophylactic gonadectomy is recommended by expert consensus in TS patients with euchromatic Y-chromosome, due to an increased risk (around 10%) of gonadoblastoma (Gravholt *et al*., 2017). The gonadectomy was recommended to P1.

In P2, the sex differentiation and a normal male external genital were possible because of the presence of *SRY* gene, despite of a 45,X lineage. The clinical variability could be strongly influenced by the concentration and distribution of the 45,X cell line in the various tissues, and the differential expression of genes located on the Y chromosome (Patsalis *et al*, 2005; Lindhardt *et al*., 2012). Males with a 45,X/46,XY karyotype and its variants seem to have a strong chance of normal testicular function (Lindhardt *et al*., 2012). However, the association of the phenotypic characteristics with the presence or absence of Y-chromosomal loci, hosting genes other than *SRY* remains uncertain (Patsalis *et al*, 2005; Lindhardt *et al*., 2012). In both patients, the absence of *XIST* on sSMC, and the early replication suggested that the sSMC was not inactivated. This may lead to different clinical outcomes, especially about mental development (Liehr *et al*., 2007). Studies in TS females have indicated that a severe phenotype and intellectual disability could be primarily caused by active partial X disomy resulting from the deletion or impaired expression of the *XIST* (Migeon *et al*., 2000).

Complex sSMC of P1 had two copies of *SHOX* gene, and patient 2 one copy. *SHOX* haploinsufficiency have been associated with short stature and various skeletal features in TS patients, such as scoliosis, high arched-palate, and micrognathia (Li *et al*., 2017). The short stature in P1 should be due the presence of a 45,X cell line.

Complex cryptic mosaicism for sSMC derived from chromosome X has been described earlier (Liehr, 2012; Santos *et al*., 2010]. Some Y-chromosome microdeletions in critical regions could provide instability on the Y-chromosome leading to the development of a 45,X cell line (Patsalis *et al*., 2005). Adikusuma *et al.* (2017) using CRISPR/Cas9 technology to remove Y chromosome sequences showed that both centromere removal and chromosome shredding induced Y chromosome loss. In both P1 and P2, the rearrangement occurred near the pseudoautosomal region; this region could be prone to rearrangements because of its sequence homology. Structural chromosome rearrangements involving both X and Y chromosomes are very unusual (Bispo *et al*., 2014). Liehr *et al.* (2013) reviewed 73 complex sSMC (excluding ES), which only three were derived from sex chromosomes, one with material from X chromosome and two with material from the Y chromosome. Although complex markers represent a small percentage (~0,9%) of sSMCs, this may be underestimated as highlighted in recent studies applying aCGH (Reddy *et al*., 2013). A complex sSMC involving both X and Y chromosomes in a TS patient in a group of 75 marker chromosomes, was reported (Li *et al*, 2020).

We present the cytomolecular characterization of two original mosaicism cases with 45,X cell lines and a complex sSMCs involving X and Y chromosomes. These findings suggest that complex sSMCs involving X and Y chromosomes could be much more frequent than previously described (Bispo *et al*., 2014).

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Conflict of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicial to the impartiality of the reported research.

Author Contributions

MBG performed the FISH and replication experiments of patient 1, interpreted the results drafted and the initial manuscript. MOF performed the FISH and replication experiments of patient 2 and interpreted the results. ISP performed PCR. ISP, EK, MMG and MGR did patient' clinical diagnosis and treatment. SAPP performed G-banding analysis. MCMR reviewed all laboratory results, participated in its design and coordination, and helped draft the initial manuscript. MGR participated in its design and coordination, and helped draft the initial manuscript.

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It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

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- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
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- Computer programs
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2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



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Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

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To make a paper clear: Adhere to recommended page limits.



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Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

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Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

INDEX

A

Adrenal · 5
Agitation · 27, 29
Amplitude · 30

C

Causative · 18
Cessation · 26, 27, 28, 30
Coagulation · 14, 15, 17

D

Depletion · 1
Duodenal · 3

E

Endure · 1

F

Febrile · 29, 33

M

Morphine · 6, 7, 8, 17

P

Precipitate · 14, 29

R

Resuscitation · 9

S

Sedation · 9, 11, 31
Susceptible · 9
Sympathetic · 5, 13, 14, 15

T

Therapeutic · 1, 17, 28





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