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GLOBAL JOURNAL OF MEDICAL RESEARCH: I
SURGERIES AND CARDIOVASCULAR SYSTEM



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Rickettsial Infections: A Clinician's Diagnostic Dilemma

By Dr. Sriranjani Iyer, Dr. Harsh Rajeev Mehta & Dr. Sarojini P. Jadhav

Abstract- Rickettsial diseases are arthropod borne zoonotic infections that are being increasingly recognized as one of the causes of pyrexia of unknown origin (PUO). These pathogens are gram-negative bacteria causing fever and rash, usually transmitted to humans by tick or flea bite. These infections must be differentiated from other febrile illnesses such as enteric fever, malaria, dengue, leptospirosis, and infectious mononucleosis. The common clinical presentation includes fever with chills and rigor, headache, vomiting, cough, conjunctival congestion and eschar. Presenting with varied and non-specific symptoms, ignorance, and low index of suspicion, they are often under-diagnosed due to the unavailability of the reliable diagnostic test. Weil- Felix test (WFT) is a non-specific heterophile tube agglutination test in which antibodies against rickettsiae are detected. If timely treatment with doxycycline is instituted the adverse consequences can be well averted.

Keywords: rickettsia, rash, fever, weil-felix test.

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Rickettsial Infections: A Clinician's Diagnostic Dilemma

Dr. Sriranjani Iyer^α, Dr. Harsh Rajeev Mehta^σ & Dr. Sarojini P. Jadhav^ρ

Abstract- Rickettsial diseases are arthropod borne zoonotic infections that are being increasingly recognized as one of the causes of pyrexia of unknown origin (PUO). These pathogens are gram-negative bacteria causing fever and rash, usually transmitted to humans by tick or flea bite. These infections must be differentiated from other febrile illnesses such as enteric fever, malaria, dengue, leptospirosis, and infectious mononucleosis. The common clinical presentation includes fever with chills and rigor, headache, vomiting, cough, conjunctival congestion and eschar. Presenting with varied and non-specific symptoms, ignorance, and low index of suspicion, they are often under-diagnosed due to the unavailability of the reliable diagnostic test. Weil- Felix test (WFT) is a non-specific heterophile tube agglutination test in which antibodies against rickettsiae are detected. If timely treatment with doxycycline is instituted the adverse consequences can be well averted.

Keywords: rickettsia, rash, fever, weil-felix test.

I. INTRODUCTION

Rickettsial diseases are some of the most covert re-emerging infections of the present times. They are notoriously difficult to diagnose; untreated cases can have fatality rates as high as 30-35% but when diagnosed properly, they are often easily treated (1). High index of suspicion is the key to early diagnosis. Fever, rash, headache, myalgia, lymphadenopathy and eschar are various clinical features of these infections.

The greatest challenge to the clinician is the difficult diagnostic dilemma posed by these infections early in their clinical course when antibiotic therapy is most effective (4). For India, the reported numbers are an underestimate due to lack of community-based data and non-availability of confirmatory laboratory tests (5). Rickettsial disease in India is documented from Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala and Tamil Nadu (1, 6).

Rickettsial infections sometimes produce severe life-threatening manifestations and takes a fulminant course. Rickettsial infections are attributed to causing pyrexia of unknown origin (PUO) and thereby require to be differentiated from other febrile illnesses such as enteric fever, malaria, dengue, leptospirosis, and infectious mononucleosis (7). No single laboratory finding is specific for early diagnosis.

Tests available to diagnose rickettsiosis are culture, serology including immunofluorescence, and molecular tests. Weil- Felix test (WFT) is a non-specific heterophile tube agglutination test in which antibodies against rickettsiae are detected using a heterophile Proteus antigen (8). Doxycycline is the drug of choice, and it can be used safely even in children below eight years of age.

We report two cases of fever with rash with a varied presentation, diagnosed to be rickettsial in origin after exclusion of other illnesses with pyrexia of unknown origin.

Case Report 1

A 6-year-old, previously healthy male child presented to the hospital with complaints of fever followed by rashes over lower extremities. He also complained of myalgia, arthralgia, and headache. Initially, these rashes were small erythematous, which soon developed into tender pustular eruptions over lower extremities, which were managed by incision and drainage. Pus from the lesion was sent for culture and antibiotic sensitivity. Pustular eruptions continued after that, and they quickly ulcerated. There was no reduction in fever spikes in the child with the maximum recorded temperature of 39.5 degree centigrade. It was associated with progressing myalgia and arthralgia. There were no pets in the family or the neighbourhood. He gives a history of playing in fields but does not recall any history of exposure to any animal or insect bite. There was no significant travel history.

Physical examination revealed a lethargic febrile child with multiple tender pustular eruptions (5-10 in number per limb), predominantly over the medial aspect of legs progressing upwards towards the trunk. These pustules showed an erythematous base. Old pustules converted into multiple undermined ulcers over the legs, with 2.5cm x 2.5cm being the largest. Inguinal lymphadenopathy over bilateral inguinal region was present with lymphnode being non-tender, enlarged, firm in consistency, 2cm x 1 cm in size, partially mobile with no superficial skin changes over the lymphnode.

The child was initially treated with empirical injectable antibiotics starting with amoxicillin and clavulanic acid, but his symptoms progressed gradually with time, with pustular eruptions progressing upwards from the lower extremities, with an increase in the number of pustules. Patient's unresponsiveness to

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various intravenous higher antibiotics lead to a detailed approach to this case with discussion among pediatrician, surgeon, dermatologist as well as a microbiologist.

The patient's leukocyte count was elevated, starting from 24000 cells per cubic mm progressed to 42000 cells per cubic mm. Other laboratory values were within normal limits. Pus culture and sensitivity persistently showed no growth. Blood culture and sensitivity was also sent before the starting of empirical antibiotics, which showed no growth. Edge biopsy of the lesion was inconclusive once and a repeat biopsy report showed focal ulceration and necrosis of the epidermis.

As a diagnosis of exclusion, as suggested by the microbiologist, Weil- Felix test was done, which was positive for Ox 19-9 with a titre of 1:320. Patient was diagnosed to have a rickettsial infection and was started on Injectable Doxycycline. There was a resolution of all symptoms, including fever, pustules, eschars, myalgia, and arthralgia. All the symptoms resolved within 7-10 days, and all laboratory values came back to the normal range within ten days. He recovered well within ten days with an uneventful hospital stay and was discharged with a split skin graft over the raw area over the medial aspect of the left foot of previous ulceration but graft was rejected.



Figure 1: Initial Pustular lesion over leg after incision and drainage



Figure 2 and 3: Multiple undermined ulcers over thigh with pus and slough covering the floor





Figure 4, 5 and 6: Healing ulcers over thigh after the start of Doxycycline



Figure 7: Healthy granulation over the medial aspect of right ankle



Figure 8: Split skin graft over the medial aspect of right ankle



Figure 9: Ulcer over right ankle post graft rejection

Case Report 2

A 4-year-old female child was brought by parents to casualty with chief complaints of swelling over the right thigh since one month. There is a positive

history of low-grade fever on and off with chills since 15 days. She had vague nonspecific symptoms. An irregular indurated swelling extending from medial aspect to posterior aspect of the right thigh of around 10

cm x 8cm in size was present, which was tender to touch with redness over the swelling.

Ultrasonography of right thigh was done, which showed an ill-defined heteroechoic collection with few dense internal echoes with no vascularity within it noted in the intramuscular plane in the right postero-medial thigh, with extensive fat stranding with diffuse subcutaneous edema giving cobble stone appearance suggestive of a non-tappable infective etiology.

The patient was taken for debridement under anaesthesia. Intraoperatively, 10ml caseous material was expressed out and sent for culture and sensitivity and CBNAAT testing. Indurated tissue specimen was sent for histopathology, which was suggestive of infected granulation tissue with exudates of neutrophils and lymphocytes. Pus culture sensitivity report showed *Staphylococcus aureus* sensitive to linezolid, cefoxitin, and clindamycin. CBNAAT report was negative for tuberculosis. She was treated with sensitive Intravenous antibiotics with regular dressings, but the wound over right thigh showed minimal improvement. Repeat debridement was done after 20 days, and wound swab culture was suggestive of *Klebsiella pneumoniae* sensitive to amikacin, cefepime, imipenem, and gentamicin. Patient was started on amikacin after that,

according to pediatric dosage. The exposed muscle showed induration and colour change and was sent for a muscle biopsy, which was suggestive of few gram-negative bacilli and pus cells.

Due to minimal improvement in the wound healing, a review opinion was taken after consulting with the panel of pathologist, microbiologist, surgeon, paediatrician and a Weil-Felix test was suggested. It was positive for OX-1, OX-2, with a titre of 1:160 for OX 19 and 1:160 for OX 2. The patient was treated for *Rickettsia*, and a course of Doxycycline was given for 14 days. Her wound was improving with a generalized improvement in the overall condition of the patient. All laboratory parameters came back to the normal range. The child was discharged, and daily dressings were advised. On Follow-up, the wound showed healthy granulation tissue. Fungal culture was present on KOH preparation. Swab culture on Sabouraud's Dextrose Agar showed features suggestive of *Trichosporon* Infection. The patient was treated with Capsule Fluconazole 150mg for three weeks and had an uneventful recovery post discharge.



Figure 10: Post first debridement nonhealing ulcer over the posterior aspect of the right thigh



Figure 11: Post second debridement intraoperative photograph of the right posterior aspect of thigh ulcer



Figure 12: X-ray photograph of the right thigh to look for bony involvement





Figure 13: Healing Ulcer over the right thigh posterior aspect at the start of Doxycycline



Figure 14: Healing Ulcer over right thigh posterior aspect after completion of course of Doxycycline



II. DISCUSSION

Rickettsial pathogens are gram-negative bacteria causing fever and rash, usually transmitted to humans by contamination of bite sites or skin abrasions with *Rickettsia*-containing flea feces or directly by the bite of ticks (9). Rickettsial infection should be suspected in the presence of above clinical features in a patient with a likelihood of tick exposure. They should undergo relevant hematological and biochemical testing, and those with a high probability of rickettsial infection should be treated with appropriate antimicrobials.

The Weil Felix test still serves as a useful and cheapest available tool for the laboratory diagnosis of rickettsial diseases. A four-fold rise in agglutinin titres in paired sera is diagnostic for infection with these febrile agents. However, with a single serum sample available, the test is suggestive of infection only at a high cut-off titre ($>1:320$) at which the positive predictive value and the specificity is reliable (10).

Rickettsial diseases can be easily confused with a variety of viral (measles, enteroviralexanthems, dengue, infectious mononucleosis), protozoal (malaria), bacterial (meningococemia, typhoid, leptospirosis, toxic shock syndrome, scarlet fever) and collagen vascular (Kawasaki disease, other vasculitis) diseases, and adverse drug reactions. Doxycycline is the drug of choice.

III. CONCLUSION

Rickettsial infections are difficult to diagnose and require consideration of clinical presentation, various environmental factors, and even the response to antibiotics. The common clinical presentation includes fever with chills and rigor, headache, vomiting, cough, conjunctival congestion and eschar. Rashes are a rare symptom(1). Persistence of fever even after 48 h, the presence of rash and tick exposure with altered biochemical parameters should alert the clinician toward rickettsial diseases (11). Rickettsial diseases, due to diagnosis of exclusion, lead to extensive investigations in children with fever of undetermined origin contributing to financial burden on families.

The fulminant course of rickettsial infections can lead to life-threatening manifestations such as disseminated intravascular coagulation, meningococcal meningitis syndrome, acute renal failure, hepatic failure, non-cardiogenic pulmonary edema, interstitial pneumonitis, and myocarditis (8).

In view of low index of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests, these infections are notoriously difficult to diagnose. Failure of timely diagnosis leads to significant morbidity and mortality. With timely diagnosis, treatment is easy, affordable and often successful with dramatic response to

antimicrobials. It is necessary to increase awareness among doctors as these infections are often the last to be suspected.

REFERENCES RÉFÉRENCES REFERENCIAS

1. Batra HV. Spotted fevers and typhus fever in Tamil Nadu – commentary. *Indian J Med Res* 2007; 126: 101-103.
2. Chapman AS, Bakken JS, Folk SM, Paddock CD, Bloch KC, Krusell A, et al. Diagnosis and management of tickborne rickettsial diseases. *MMWR Recomm Rep* 2006; 55: 1-27.
3. Chugh TD. Emerging and reemerging bacterial diseases in India. *J Biosci* 2008; 33: 549-555.
4. Mahajan SK, Kashyap R, Kanga A, Sharma V, Prasher BS, Pal LS. Relevance of Weil-Felix test in diagnosis of scrub typhus in India. *J Assoc Phys India* 2006; 54: 619-621.
5. Mathai E, Lloyd G, Cherian T, Abraham OC, Cherian AM. Serological evidence of continued presence of human rickettsiosis in southern India. *Ann Trop Med Parasitol* 2001; 95: 395-398.
6. Sundhinda BK, Vijaykumar S, Kutti AK. Rickettsial spotted fevers in Kerala. *Natl Med J India* 2004; 17: 51-52.
7. Kalra SL, Rao KN. Typhus fevers in Kashmir State. Part II. Murine typhus. *Indian J Med Res* 1951; 39:297-302.
8. Rathi, N., & Rathi, A. (2010). *Rickettsial infections: Indian perspective. Indian Pediatrics, 47(2), 157–164.* doi:10.1007/s13312-010-0024-3
9. Azad AF. Epidemiology of murine typhus. *Annu Rev Entomol.* 1990; 35: 553–569. doi: 10.1146/annurev.en.35.010190.003005.
10. Kamarasu K, Malathi M, Rajagopal V, Subramani K, Jagadeeshramasamy D, Mathai E. Serological evidence for wide distribution of spotted fevers and typhus fever in Tamil Nadu. *Indian J Med Res* 2007; 126: 128-30.
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A Comparative Study to Ascertain the Efficacy of Palonosetron, Granisetron and Metoclopramide in Preventing Post-Operative Nausea and Vomiting in Patients Undergoing General Anaesthesia for Ear, Nose and Throat Surgeries

By Dr. Jasmine Kaur & Dr. Farah Husain

Introduction- Postoperative nausea and vomiting (PONV) can be a very distressing side effect following general anaesthesia. Patients and health care professionals report the avoidance of PONV is of equal or sometimes even greater concern than avoidance of postoperative pain.¹ It can result in increased morbidity, delay in hospital discharge and unexpected hospital re-admission, thereby increasing the total medical costs². Moreover, PONV has been a major cause of decreased patient satisfaction³. There are several physiologic complications of nausea and vomiting that are of concern to the anaesthesiologist. Some of them being visceral wound dehiscence, electrolyte disorders, raised venous pressure leading to bleeding, rise in intraocular and intracranial tension and aspiration pneumonia especially in the sedated post-operative patient.

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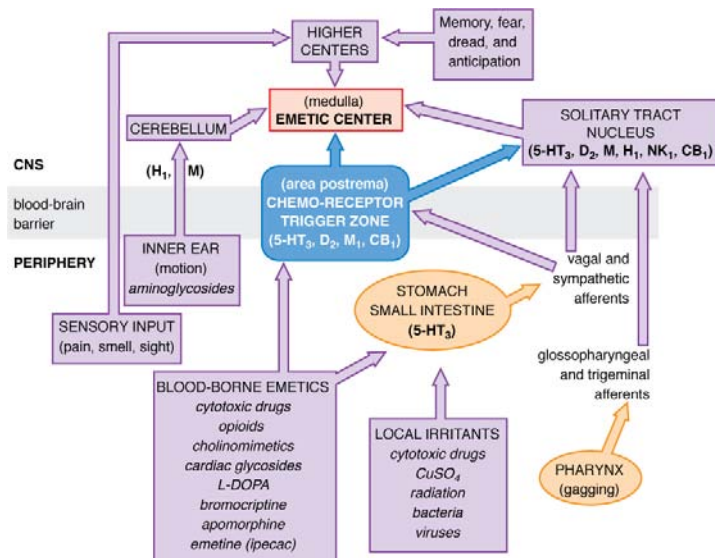
Dr. Jasmine Kaur ^α & Dr. Farah Husain ^ο

I. INTRODUCTION

Postoperative nausea and vomiting (PONV) can be a very distressing side effect following general anaesthesia. Patients and health care professionals report the avoidance of PONV is of equal or sometimes even greater concern than avoidance of postoperative pain.¹ It can result in increased morbidity, delay in hospital discharge and unexpected hospital re-admission, thereby increasing the total medical costs². Moreover, PONV has been a major cause of decreased patient satisfaction³. There are several physiologic complications of nausea and vomiting that are of concern to the anaesthesiologist. Some of them being visceral wound dehiscence, electrolyte disorders, raised venous pressure leading to bleeding, rise in intraocular and intracranial tension and aspiration pneumonia especially in the sedated post-operative patient.

PONV is influenced by multiple factors such as the patient itself, surgery and anaesthesia related factors and involves release of 5-hydroxytryptamine (5-HT) in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract (Figure 1). The 5-HT subtype3 (5-HT₃) receptors participate selectively in the emetic response. The risk and incidence of PONV increases with post-operative opioid use³ but has been found to be decreased in smokers as compared to non-smokers⁴. On the other hand, its incidence increases in patients with history of motion sickness and after consumption of alcohol.

Certain surgical procedures like gynaecological, abdominal specially gastro intestinal, laparoscopic surgeries, ENT surgeries and ophthalmic surgeries are more likely to lead to PONV because of stimulation of vagal afferents during manipulation.⁵



Source: Brunton LL, Chabner BA, Knollmann BC: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition; www.accessmedicine.com
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Figure 1

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Advances in PONV prophylaxis over recent years include use of non-pharmacological measures to reduce baseline risk, a change to less emetogenic anaesthetic techniques and the use of newer antiemetic drugs. However, the use of antiemetics, either alone or in combination, remains the mainstay in PONV management. Drugs used include metoclopramide, haloperidol, dexamethasone and the selective 5-HT₃ receptor antagonists. The last group is now a first line option because of its effectiveness and general lack of adverse drug reactions.⁶ Most clinical researches with the 5-HT₃ receptor antagonists have used ondansetron, and its antiemetic efficacy is well established in chemotherapy-induced emesis and in the treatment and prevention of PONV. However, several alternatives to ondansetron e.g. granisetron, tropisetron, dolasetron, ramosetron are also available now. Palonosetron, approved by the Drugs Controller General of India on 25.04.2009, is the most recently introduced member in this class of drug. Its interaction pattern with the 5-HT₃ receptor is different from earlier 5-HT₃ receptor antagonists, enabling a higher binding affinity and longer half-life.

We compared the antiemetic effectiveness of intravenous Palonosetron, administered as a single pre-induction dose, in ear, nose and throat surgeries during the first 48 postoperative hours with another 5-HT₃ receptor antagonist Granisetron and a commonly used Dopamine agonist, Metoclopramide.

Palonosetron is a novel 5HT₃ receptor antagonist, first approved for the prevention of chemotherapy induced nausea and vomiting. It has greater binding affinity and longer biological half-life than older 5HT₃ receptor antagonists.⁸ It has been suggested that 5HT₃ receptors are found in the gut and in areas of central nervous system associated with the regulation of nausea and vomiting; being abundant in the CTZ which has projections to the vomiting centre located in the lateral reticular formation of medulla oblongata⁵. Palonosetron has been compared with placebo for the prevention of PONV in patients undergoing open abdominal and gynaecological surgery⁸. Comparison with other antiemetic drugs and in other types of surgery is still limited. Drowsiness, headache cardiac rhythm disturbances are a few side effects.

Granisetron is a selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT₁; 5-HT_{1A}; 5-HT_{1B/C}; 5-HT₂; for α 1-, α 2-, or β -adrenoreceptors; for dopamine-D₂; or for histamine-H₁; benzodiazepine; picrotoxin or opioid receptors. The differences between these drugs could stem from differences in pharmacokinetics or receptor binding profiles.

Metoclopramide has been available for about 40 years, is cheap, and is widely used for treatment and prevention of nausea and vomiting. Metoclopramide has

multiple sites of action. It is a prokinetic drug that acts by increasing the tone of the lower oesophageal sphincter. It also has an anti-dopaminergic action on the chemoreceptor trigger zone and at higher doses has an anti-serotonergic activity.^{9,10}

II. PATIENTS AND METHODS

After obtaining approval from the institutional ethical committee, written informed consent was taken from the patient one day prior to the scheduled surgery. A total of 90 adult patients of ASA I and II group, having one or both risk factors for PONV-prior history of PONV, Non-smoker, female gender, use of opioids in peri-operative period, scheduled to undergo Ear, Nose or Throat operations under general anaesthesia were selected and randomised in a double blind manner by computer generated algorithm. Patients were to receive either Inj. Palonosetron 0.075mg iv (Group P, n=30), Inj. Granisetron 1 mg (Group G, n=30) or Inj. Metoclopramide 10 mg iv (Group M, n =30) 15 minutes before induction of anaesthesia. Saline solution was added to bring the total volume of all the drugs to 5 ml.

Exclusion Criteria:

- Patients within ability to understand or cooperate with the study procedures as determined by the investigator
- Pregnant women
- Nursing or planning to become pregnant women
- Cancer patient who had chemotherapy within 4 weeks prior to study entry
- Any kind of emetogenic radiotherapy taken within 8 weeks prior to study entry
- Consumption of any investigational drugs within 30 days before study entry
- Consumption of any drug with potential antiemetic efficacy within 24 hours prior to anaesthetic procedures
- Any vomiting, retching, or nausea in the 24 hours preceding the administration of anaesthesia,
- Body Mass Index (BMI) >40
- Suspected / current history of alcohol abuse or drug abuse known hypersensitivity/ contraindication to 5-HT₃ antagonist or study drug excipients
- Epileptic patients
- Patients receiving other drugs which are likely to cause extrapyramidal reactions were excluded from the study.

All patients were pre-oxygenated for 3 minutes with 100% oxygen. Premedication was done by using Inj. Glycopyrrolate 0.2 mg iv, Inj. midazolam 1 mg iv and Inj. fentanyl 2 microgram/kg iv. Patients were induced with was Inj Thiopentone sodium (4-7 mg/kg) iv. Injection Vecuronium 0.1 mg/kg iv was used to facilitate Endotracheal intubation. Anaesthesia was maintained with O₂ + N₂O + Isoflurane. Muscle relaxant used for

maintenance was Inj. Vecuronium bromide 0.02 mg/kg iv. In the intra-operative period, multimodal analgesia was achieved with Injection Paracetamol 1gm iv. At the completion of surgery, once patients had regained attempts of spontaneous breathing, they were given reversal with Inj. neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.01 mg/kg.

After completion of surgery, patients were shifted to post-operative anaesthesia care unit where pain was controlled by Inj. Diclofenac sodium 75 mg IM 8 hourly or on patient demand and monitored for the incidence of nausea and vomiting according to Visual Analogue Scale (0-no nausea, 10- worst nausea) at 0-2 hrs, 2-6 hrs, 6-12 hrs, 12-24 hrs, 24-48 hrs, incidence of adverse effects in all the three groups, use of rescue antiemetic in the three groups and for patient satisfaction to the given drugs in all the three groups. Rescue Antiemetic was given when one episode of PONV occurred or at VAS >5 and the patient requested treatment. A complete response was defined as the absence of PONV and no use of rescue antiemetics. Inj. Palonosetron 0.075 mg was used as a rescue antiemetic in Group M and Inj. Metoclopramide 10 mg IV was used as a rescue antiemetic in Group P & Group G.

III. STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). The statistical observations of the categorical variables were evaluated by using Chi square test and Independent student t test. The observed side effects and risk factors were analysed with Fisher's exact test. The observational results are expressed mainly Mean + SD or number (%)

A P value < 0.05 was considered statistically significant.

IV. RESULTS

The study groups were comparable demographically. There was no significant difference in the duration of surgery among groups (Table 1 & Graph 1). The intraoperative hemodynamic parameters were also comparable.

Incidence of Nausea in Post-operative Period

Group P was found to have much less nausea as compared to the other groups ($p < 0.05$) as per Table 2.

Incidence of Vomiting in Post-operative Period

As there was no significant difference in incidence of vomiting in any of the three groups in 48 hours post-operative period as shown in Table 3, the drugs are comparable in their efficacy to prevent vomiting.

Subjective Assessment of Patient's Satisfaction

There was a significant difference in the satisfaction rate in Group P as compared to Group M (Graph 2).

Use of Rescue Medication in Post-operative period

There was no significant difference while comparing the need of rescue anti-emetic in Palonosetron and Granisetron group but a statistically significant p value ($p < 0.05$) was obtained while comparing Metoclopramide with Palonosetron ($p = 0.009$) and Granisetron ($p = 0.024$) as depicted in Table 4 and Graph 3.

Side Effects Profile: On comparison of side effects among three groups, in Group P, 3 patients complained of headache in 48 hours while 2 patients complained of headache in Group G and 1 patient in Metoclopramide Group implying no significant difference in side effects among the three groups. Similarly, after comparison of other side effects of 5HT₃ antagonists like dizziness, constipation and myalgia there was no significant difference in the incidence of side effects in the three groups. All events were of mild severity and settled spontaneously without separate treatment. There was no instance of corrected QT interval prolongation ($QT_c > 450$ milliseconds) in either of the study groups. (Graph IV)

V. DISCUSSION

Postoperative nausea and vomiting (PONV) is a common complication following surgery under general anaesthesia. Incidence of PONV is 30-40% in normal population undergoing general anaesthesia while the incidence touches a peak of 75-80% in certain high risk groups². The postoperative period is associated with variable incidence of nausea and vomiting depending on the duration of surgery, the type of anaesthetic agents used (dose, inhalational drugs, opioids), smoking habit etc⁴. 5HT₃ receptor stimulation is the primary event in the initiation of vomiting reflex¹⁶. Anaesthetic agents trigger this reflex by stimulating the central chemoreceptor trigger zone (CTZ) and also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5 HT₃ receptors on the vagus afferent fibres⁷. Our objective was to compare two different groups of antiemetics, in a high-risk group of patients undergoing ear, nose and throat surgeries.

On comparison of overall incidence of nausea among the three groups at 0-48 hrs, Palonosetron was found to be most efficacious in this study. The incidence of nausea was only 33.33% in palonosetron group as compared to 60% in Granisetron group and 90% in Metoclopramide group which was found to be statistically significant ($p < 0.05$). But there was no difference in the overall incidence of vomiting per se between the three groups.

In a similar study done by Bhattacharjee et al¹¹, they reported that prophylactic therapy with palonosetron is more effective than granisetron for prevention of PONV after laparoscopic cholecystectomy during the 24-48hour post-operative period, though not in the first 24 hours and both are devoid of clinically important side effects as established in our study.

Oksuz et al¹² did a similar study and evaluated the effectiveness of Metoclopramide, Ondansetron and Granisetron in the prevention of nausea and vomiting after laparoscopic cholecystectomy. They found that the drugs had similar antiemetic effect in the first 3hour post-operative period but during 4-24 hour, Granisetron resulted in a significantly lower incidence of PONV than metoclopramide and ondansetron, whereas metoclopramide was ineffective.

Similar results were obtained by K. Gupta et al¹³ They did a prospective randomised study to compare Palonosetron, Ondansetron and Granisetron for antiemetic prophylaxis of postoperative nausea and vomiting and found that Palonosetron was comparatively highly effective than Granisetron to prevent the PONV after anaesthesia due to its prolonged duration of action.

Fujii et al¹⁴ also found similar results in their study while comparing Granisetron, droperidol and metoclopramide in the treatment of established nausea and vomiting after breast surgery. They found that 88% of patients were emesis free in Granisetron group whereas only 56% patient were emesis free in Metoclopramide group, p value = 0.025.

In a randomised controlled trial in middle ear surgeries by Basu et al¹⁵, a single dose of Palonosetron was found to be a superior anti-emetic to Granisetron or Ondansetron in complete prevention of postoperative nausea and vomiting during the first 24 hours period.

Inj. Metoclopramide 10mg iv was used as rescue antiemetic in Group P and Group G. In Group P 13.4% patients received rescue antiemetic while in Group G, 16.7% patients received rescue antiemetic. Inj. Palonosetron 0.075 mg was used as rescue antiemetic in Group M. 43.4% patients received rescue antiemetic in Group M. There is no significant difference while comparing Palonosetron and Granisetron group but a statistically significant p value (p value <0.05) was obtained while comparing Metoclopramide with Palonosetron (p = 0.009) and Granisetron (p= 0.024) which suggests that they are superior in preventing PONV than metoclopramide.

After completion of 48 hours of post-operative period, we asked the patients about the satisfaction to the given drug in all the three groups. In group P, 60% patients were satisfied, in Group G 50% patients were satisfied and in Group M, 36.7% were satisfied from the given drug and p value is < 0.05 when Group P was compared with Group M and while comparing Group G with Group M. It shows there is a significant difference in

patient satisfaction when Group M was compared to rest of the groups with maximum satisfaction rate in Group P, implying that Palonosetron has better control in preventing PONV than Granisetron and Metoclopramide.

VI. CONCLUSION

Palonosetron, the newer 5 HT₃ antagonist is more efficacious than Granisetron and Metoclopramide especially after 24 hours of surgery with more satisfaction score and less incidence of nausea and vomiting. So, if easily available, palonosetron may be considered more routinely in patients undergoing high risk surgeries for PONV.

Since our study was on smaller group of patients, to ascertain an overall potency of the newer drugs, a larger study population needs to be considered. Complications related to surgery such as stimulation of stapes leading to severe post-operative nausea were not considered while evaluating the data.

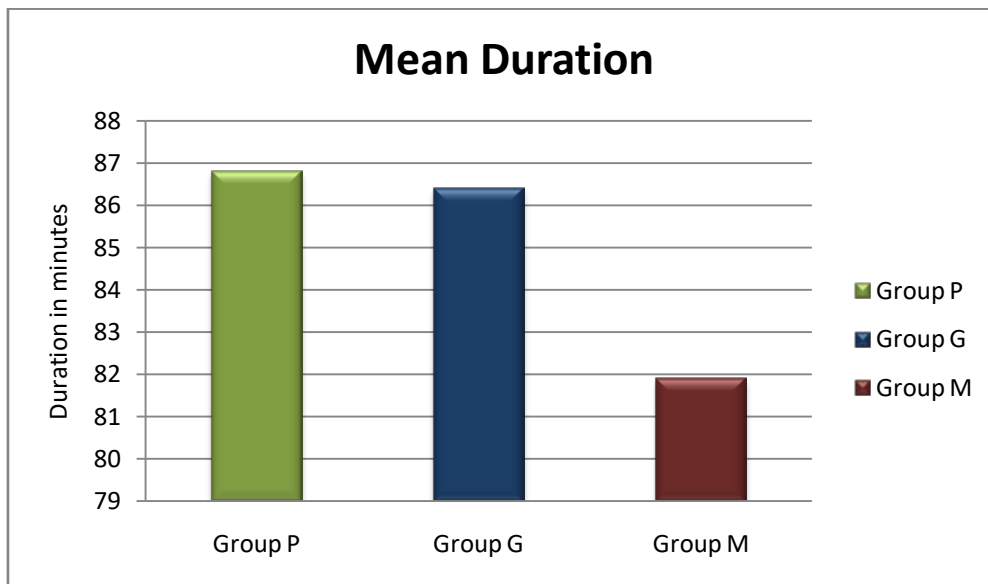
REFERENCES RÉFÉRENCES REFERENCIAS

1. Grover VK, Mathew PJ, Hegde H. Efficacy of orally disintegrating ondansetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: A randomised, double-blind placebo controlled study. *Anaesthesia*. 2009; 64:595–600.
2. Islam S, Jain PN. Post-operative nausea and vomiting (PONV): A review article. *Indian J Anaesth*. 2004; 48:253–8.
3. Turkistani A, Abdullah K, Manaa E, Delvi B, Khairy G, Abdulghani B, et al. Effect of fluid preloading on postoperative nausea and vomiting following laparoscopic cholecystectomy. *Saudi J Anaesth*. 2009; 3:48–52.
4. Park JW, Jun JW, Lim YH, Lee SS, Yoo BH, Kim KM et al. The comparative study to evaluate the effect of palonosetron monotherapy versus palonosetron with dexamethasone combination therapy for prevention of post-operative nausea and vomiting. *Korean J Anesthesiol* 2012.
5. Gan TJ Risk factors for post operative nausea and vomiting. *AnesthAnalg*. 2006; 102: 1884-98.
6. Wallenborn J, Eberhart LH, Kranke P. Postoperative nausea and vomiting – what's new in anti-emetic pharmacotherapy. *Anesthesiol Intensiv med Notfall med Schmerzther*. 2009; 44:296–304.
7. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment and prevention. *Anesthesiology* 1992; 77:162-84.
8. Rojas C, Stathis M, Thomas AG, Massuda EB, Alt J, Zhang J, et al. Palonosetron exhibits unique molecular interactions with the 5-HT₃ receptor. *Anesth Analg*. 2008; 107:469–78.

9. Ho KY, Gan TJ. Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. *Curr Opin Anaesthesiol* 2006; 9:606-11.
10. Ho KY, Gan TJ. Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. *Curr Opin Anaesthesiol* 2006; 9:606-11.
11. Bhattacharjee DP, Dawn S, Nayak S, Roy PR, Acharya A, Dey R. A comparative study between palonosetron and granisetron to prevent postoperative nausea and vomiting after laproscopic cholecystectomy. *J Anaesthesiol Clin Pharmacol* 2010; 26:480-3.
12. Oksuz H, Zencirci B, Ezberci M. Comparison of the effectiveness of metoclopramide, ondansetron, and granisetron on the prevention of nausea and vomiting after laparoscopic cholecystectomy. *J Laparoendosc Adv Surg Tech A*. 2007 Dec;17:803-8
13. Gupta K, Singh I, Gupta PK, Chauhan H, Jain M, Rastogi B. Palonosetron, Ondansetron, and Granisetron for antiemetic prophylaxis of postoperative nausea and vomiting- A comparative evaluation. *Anesth Essays Res* 2014; 8:197-207.
14. Fujii Y¹, Tanaka H, Kawasaki T. A Comparison of granisetron, droperidol and metoclopramide in the treatment of established nausea and vomiting after breast surgery: a double blind, randomised, controlled trial. *Clin Ther*. 2003; 25:1142-9.
15. Basu A, Saha D, Hembrom BP, Roy A, Naaz A. Comparison of palonosetron, Granisetron and Ondansetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery. *J Indian Med Assoc*. 2011; 109:327-9.
16. Bruce KT, Tyres MB. The role of 5HT₃ receptor in postoperative nausea and vomiting. *Br J Anaesth* 1992; 69:60-2.

Table 1: Demographic data

| | Group P | Group G | Group M |
|---------------------------|---------------|---------------|---------------|
| Age (yrs) | 33.73 ± 12.65 | 32.62 ± 12.33 | 29.96 ± 12.22 |
| Gender (M:F) | 17 : 13 | 16 : 14 | 17 : 13 |
| Weight (kgs) | 50.06 ± 14.43 | 51.16 ± 7.18 | 50.03 ± 6.09 |
| Duration of Surgery (min) | 86.8 ± 11.2 | 86.46 ± 11.09 | 81.96 ± 11.6 |



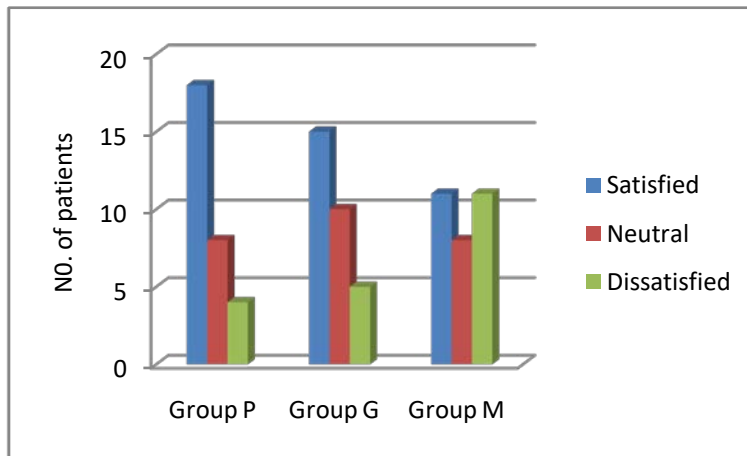
Graph 1: Mean duration of Surgery

Table 2: Incidence of Nausea in Post-operative Period

| Time (hr) | GROUP P | GROUP G | GROUP M | GROUP P VS GROUP G | GROUP G VS GROUP M | GROUP P VS GROUP M |
|-----------|---------|---------|---------|--------------------|--------------------|--------------------|
| 0-2 | 1 | 1 | 2 | p = 1 | p = 0.553 | P = 0.553 |
| 2-6 | 2 | 3 | 2 | p = 0.640 | p = 0.640 | P = 1 |
| 6-12 | 2 | 2 | 5 | p = 1 | p = 0.227 | P = 0.227 |
| 12-24 | 3 | 4 | 7 | p = 0.687 | p = 0.316 | p = 0.165 |
| 24-48 | 2 | 8 | 11 | p = 0.037 | p = 0.405 | p = 0.014 |

Table 3: Incidence of Vomiting in Post-operative Period

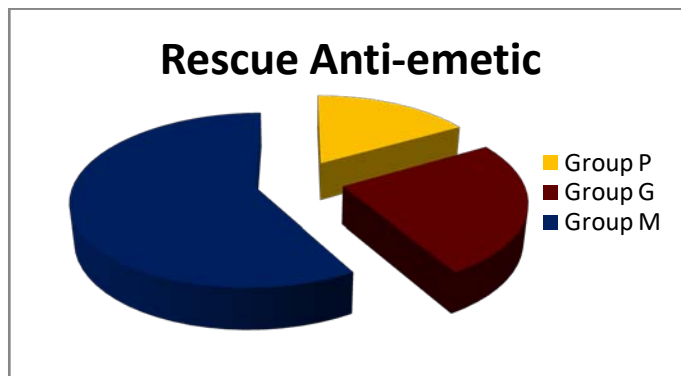
| Time (hr) | Group P | Group G | Group M | Group P VS Group G | Group G VS Group M | Group P VS Group M |
|-----------|---------|---------|---------|--------------------|--------------------|--------------------|
| 0-2 | 0 | 0 | 0 | p= 0 | p= 0 | p= 0 |
| 2-6 | 0 | 0 | 1 | p= 0 | P = 0.313 | p = 0.313 |
| 6-12 | 0 | 1 | 1 | p = 0.313 | p = 1 | P = 0.313 |
| 12-24 | 1 | 1 | 2 | p = 1 | p = 0.55 | p = 0.55 |
| 24-48 | 2 | 3 | 5 | p = 0.64 | p = 0.44 | P = 0.22 |



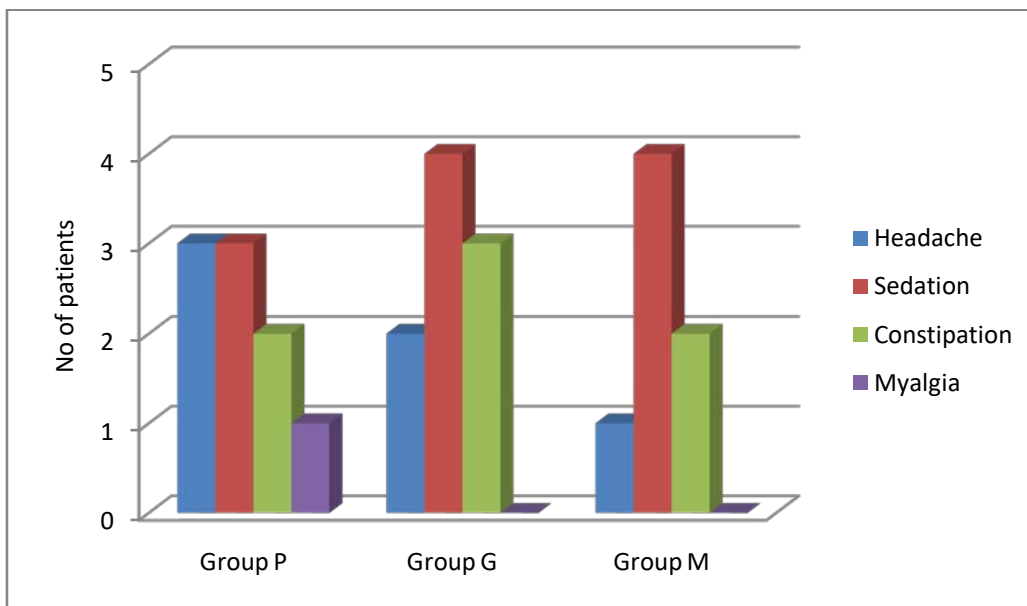
Graph 2: Subjective Assessment of Patient's Satisfaction

Table 4: Use of Rescue Medication in Post-operative period

| | Group P | Group G | Group M | Group P VS Group G | Group G VS Group M | Group P VS Group M |
|-------------------------------------------|----------|----------|-----------|--------------------|--------------------|--------------------|
| No of patient receiving rescue medication | 4(13.4%) | 5(16.8%) | 13(43.4%) | P = 0.717 | P = 0.024 | P = 0.009 |



Graph 3: Need for rescue anti-emetic in the three groups



Graph 4: Side effect profile



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Immune Status Creative Analysis in Patients after Coronary Artery Bypass Surgery (CABS) with the use of Cardiopulmonary Bypass (CPB) Machine

By Barsukov, A.A., Zemskov, V.M., Pronko, K.N., Kozlova, M.N., Shishkina, N.S., Demidova, V.S., Popov, V.A., Plotnikov, G.P., Korostelev, A.N., Kazennov, V.V., Zemskov, A.M., Sadiykov A.L. & Revishvili A.Sh.

Abstract- An analysis of the immune status in 53 patients that underwent coronary artery bypass grafting under cardiopulmonary bypass was carried out in the preoperative period and on day 1 and 7 after the surgical intervention. Significant changes in innate and adaptive immunity were revealed. In the first case, they were expressed as an inflammatory process developed throughout the postoperative period; it was confirmed with an increase in leukocytes, total and stab granulocytes, monocytes, oxidative stress of phagocytes, CD64+ and CD40+ granulocytes, endogenous intoxication with the developed significant deficiency in CD4+ monocytes, and regulatory NK cells; while immediately after the surgery, it was confirmed by IgG and IgM levels. Some changes in adaptive immunity manifested through its activation, confirmed by an increased CD4+, CD11b+, HLA-DR+, and CD4+CD25+ lymphocyte content, together with a deficiency noted in total lymphocytes and CD8+ lymphocytes.

Keywords: CABS under CPB, immune system, immunovenin.

GJMR-I Classification: NLMC Code: WG 595



IMMUNE STATUS CREATIVE ANALYSIS IN PATIENTS AFTER CORONARY ARTERY BYPASS SURGERY CABS WITH THE USE OF CARDIOPULMONARY BYPASS CPB MACHINE

Strictly as per the compliance and regulations of:



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Immune Status Creative Analysis in Patients after Coronary Artery Bypass Surgery (CABS) with the use of Cardiopulmonary Bypass (CPB) Machine

Barsukov, A.A. ^α, Zemskov, V.M. ^σ, Pronko, K.N. ^ρ, Kozlova, M.N. ^ω, Shishkina, N.S. [¥], Demidova, V.S. [§], Popov, V.A. ^χ, Plotnikov, G.P. ^ν, Korostelev, A.N. ^θ, Kazennov, V.V. ^ζ, Zemskov, A.M. ^ε, Sadiykov A.L. [€] & Revishvili A.Sh. ^ƒ

Abstract- An analysis of the immune status in 53 patients that underwent coronary artery bypass grafting under cardiopulmonary bypass was carried out in the preoperative period and on day 1 and 7 after the surgical intervention. Significant changes in innate and adaptive immunity were revealed. In the first case, they were expressed as an inflammatory process developed throughout the postoperative period; it was confirmed with an increase in leukocytes, total and stab granulocytes, monocytes, oxidative stress of phagocytes, CD64+ and CD40+ granulocytes, endogenous intoxication with the developed significant deficiency in CD4+ monocytes, and regulatory NK cells; while immediately after the surgery, it was confirmed by IgG and IgM levels. Some changes in adaptive immunity manifested through its

activation, confirmed by an increased CD4+, CD11b+, HLA-DR+, and CD4+CD25+ lymphocyte content, together with a deficiency noted in total lymphocytes and CD8+ lymphocytes. These data are deemed to be fundamentally important since they were found before the patients were discharged and could persist in the future while being associated with an unknown outcome to be investigated in the long run. Immediately after a surgical intervention to a limited number of patients, the official IgG preparation (Immunovenin) was administered by six intravenous infusions to exert a corrective effect (mainly on the innate immunity) that was truly more significant than that in patients not having received the drug. By the time of discharge, patients have a reduced content of leukocytes, granulocytes, monocytes, CD40+ granulocytes, endogenous intoxication, together with the number of patients suffering from IgG deficiency reduced. It restored the initial level of sharply increased stab granulocyte content. The significance of the data obtained is being discussed.

Keywords: CABS under CPB, immune system, immunovenin.

I. INTRODUCTION

The existing paradigm of the negative effect exerted on the immune system against the background of a heart and blood vessel pathology is beyond dispute [1]. Studies carried out in this matter have shown a significant effect exerted on the cardiovascular system status by immune cells. The main participants of the “negative process” were found to be innate immunity cells (i. e. neutrophils, monocytes) and adaptive immunity [T-lymphocytes, etc.] [2,3].

Significantly, neutrophils and monocytes represent a heterogeneous population of cells, consisting of several subpopulations, differentiated by their functional properties [4-7, 9]. Moreover, being the main cells of innate immunity, neutrophils function in two aspects relative to the cardiovascular system.

First, neutrophil in myocardial infarction promotes the transformation of M1 macrophage subpopulation (with pro-inflammatory properties) into M2 macrophage subpopulation (with anti-inflammatory and regenerative functions) [8], becoming an accomplice in the myocardial cell function recovery.

Secondly, neutrophils have significant cytotoxic potential, thus providing methods to damage the blood

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vessel endothelium [10] and cardiomyocytes [11]. A similar aggressive action attributed to neutrophils can be expected during heart surgery, especially in the case of CABS under CPB. Therefore monitoring of this process is required, as well as an in-depth selection of immunotropic drugs to level the pathological reaction.

At the same time, monocytes also consist of several subpopulations with different functional properties affecting the vessels and heart in different ways [12,13]. These are "classical" ones showing high pro-inflammatory, phagocytic, and antitumor activity, together with the production of oxygen radicals. "Intermediate" ones are those, featuring high phagocytic and pro-inflammatory activity, producing oxygen radicals, participating in the angiogenesis and proliferation of T cells; and "non-classical" anti-inflammatory ones are those having virtually no phagocytosis and producing no oxygen radicals; they monitor the state of blood vessels, wound healing, and damaged tissues, tumorigenesis, and determine the stimulation and proliferation of T cells [14]. Otherwise, they have the opposite effect.

Therefore, based on these considerations, the analysis of monocyte subpopulation in patients is of undeniable importance for studying the pathogenesis-related to various diseases, including heart and blood vessel pathologies [13, 15–20]. The studies are not given in this paper. However, we paid great importance to them and are currently studying this problem intensively.

Even though the violation of adaptive immunity during cardiac surgery (incl. CABS, etc.) is also reflected in the literature [21–24], its nature is nevertheless multidirectional, which is especially true for open-heart surgery under cardiopulmonary bypass. Moreover, in this aspect, many issues regarding the state of the immune system, the nature of its disorders, and the correlation between the indicators attributed to innate and adaptive immunity are not well studied.

For the reasons mentioned, we focused on the study of congenital and adaptive immunity in cardiac operations under cardiopulmonary bypass, since in the patients having undergone surgery, the early postoperative period is accompanied by an aseptic systemic inflammatory response, which is 6 to 20% can initiate organ failure with a high mortality rate. The main goal of our research was to study the key cells of the mentioned immunity types with their expanded phenotypic and functional characteristics, some of which have not yet been studied. Also, attempts have been made to correct immune disorders using some immunotropic drugs.

II. MATERIALS AND METHODS

Fifty-three patients, aged 48 -77 years, were enrolled in the study. The CPB time was 108 minutes

(71-168 minutes), the aortic clamping time was 51 minutes (33-84 minutes).

The blood for leukocytes was collected in tubes with K₃EDTA, and for immunoglobulins, in the specific tubes, which were then centrifuged to obtain the serum.

Leukocytes phenotyping was performed on a FACSCalibur flow laser cytofluorimeter (BD, USA). The antibodies for the leukocytes membrane antigens analysis were obtained from BD Biosciences, Becton, Dickinson, San Joe, CA, USA, Beckman Coulter in the following range: CD3, CD4, CD8, CD11b, CD14, CD16, CD21, CD25, CD45, CD64, CD40, HLA-DR. CD56 and isotypic controls, FITC, and PE, were purchased from BD, USA.

The cells were incubated with the antibodies in whole blood in the dark for 30 min at 40 C; then it was lysed with a BD FACS lysing solution and washed by centrifugation.

The analysis of the immunoglobulin isotypes (IgG, IgA, IgM) was performed using the monospecific antiserum manufactured by BioSystems (Spain), by the turbidimetric method on a semiautomated biochemical analyzer Screen Master Plus (Hospitex Diagnostics S. A., Sesto Fiorentino, Italy) at the wavelength of 340 nm. Oxygen metabolism in phagocytic cells was analyzed (on a multiple Synergy 2 SLAD detector-analyzer, Winooski, Vermont, USA) with chemiluminescence, adding luminol or lucigenin used to detect generated reactive oxygen species (ROS) to enhance the chemiluminescence reaction. The reaction was conducted in wells in volume 150 μL of luminol or lucigenin solution, 25 μL of suspension of opsonized zymosan, and 5 μL of whole blood of patients. Four repeated blood samples were used. Oxygenation in the presence of luminol supports the determination of the intracellular generation of a reactive oxygen intermediate [25]. In the case with the presence of lucigenin only, the extracellular generation of superoxide oxygen anion was detected [26].

Immunovenin was used in a group of patients (n=18), at a dose of 50 ml intravenously (2.5 g of protein), six infusions in a row.

GraphPad Prism 7 software was used for the statistical analysis. The paired and unpaired t-tests were used in work. The data obtained are presented as mean value ± standard error of the mean. Pearson's χ^2 criterion was also used. The results were considered reliable at $p < 0.05$ or less.

This study is not a clinical trial. Therefore, all items do not require a response, since the studies were carried out within the framework of permitted surgical and immune methods. Sponsors did not participate in the design, execution, interpretation, or writing of the research or writing. All subjects gave their informed consent to inclusion before they participated in the study. All clinical, laboratory, and immune studies were

carried out under the ethical standards of the Helsinki Declaration. The study protocol contained ethical aspects and information on how the principles of the Helsinki Declaration are ensured.

III. RESULTS AND THEIR DISCUSSION

a) Quantitative assay of innate immunity cells in patients after CABS under CPB

An extended analysis of cell markers (37 cell antigens) in patients after CABS under CPB was performed. The selected parameters reflect the main innate and adaptive immunity characteristics and reliably reveal one's immune status. Differences in immune parameters were determined by comparing the immune values of markers 1 and 7 days after surgery with preoperative indicators. Note that almost all immune parameters in the preoperative period did not significantly differ from the physiological norms. Therefore, the problem of any concomitant diseases

was not of great significance, since otherwise, it would have significantly affected the immune status indicators.

At the beginning of the study, it was established that in patients after CABS, the bloodstream innate immunity cell number was significantly increased. Figure 1 shows the dynamics of changes in leukocytes (A), neutrophils (B, C), and monocytes (D) in patients before surgery, on days 1 and 7 after it. As it turned out, the number of leukocytes increased sharply on the 1st day after the surgery ($p=0.0001$) and remained high until the seventh day compared to the preoperative value ($p=0.0001$).

The analysis of neutrophils - granulocytes and stabs in patients after CABS under CPB showed a significant increase in cells in the peripheral blood on days 1 and 7 (Fig. 1B, C), the absolute level of monocytes during the analysis periods also significantly exceeded its preoperative values ($p=0.0001$).

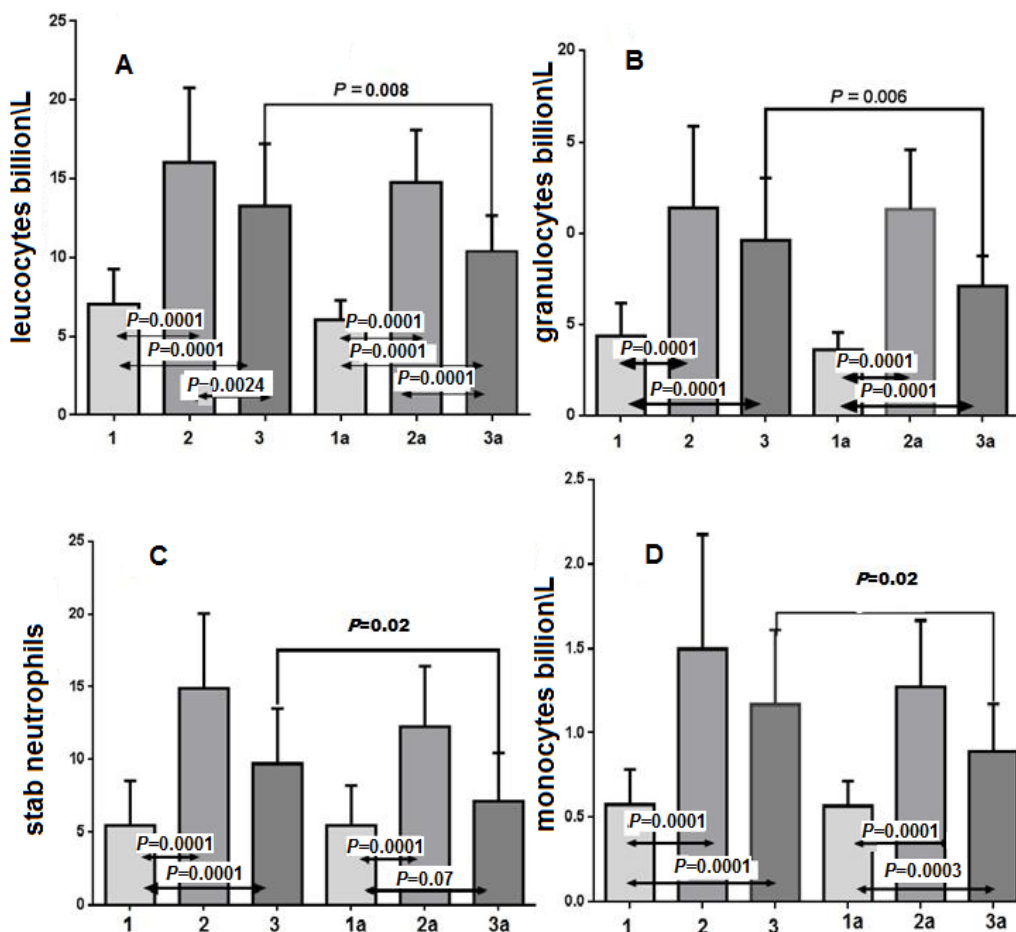


Figure 1: Increase in leukocytes (A) and innate immunity cells levels (B, C, D) in patients after CABS under CPB.

1 - before surgery, 2 - 1 day after the surgery, 3 - 7 days after the surgery. Abbreviation - a - patients who received Immunovenin

The absolute value of monocytes in the peripheral blood flow in patients after CABS under CPB (Fig. 1D) also significantly exceeded the value before surgery by the 1st ($p=0.0001$) and 7th days ($p=0.0001$).

b) Quantitative assay of cell-surface antigens in patients after CABS under CPB

The use of various markers (antibodies) is widely applied in the immune status monitoring in heart

surgery [21]. First of all, the most important is the monitoring of neutrophils and the monocytic population of phagocytes, since, during heart surgery, their activity is often negative. In our studies, we further showed significant changes in the functional properties of neutrophils and monocytes in patients after CABS. In Fig. 2, the results reflecting these changes are represented. As it turned out, on the 1st day after the surgery, the number of neutrophils with the membrane high-affinity Fc_γ receptor (CD64) expression increased significantly. It is significant that the conditions after the surgery were sterile, which most likely reflects the stress activation of the cell (Fig. 2A). On day seven, this marker returned to the preoperative level ($p > 0.05$).

The functional activity of phagocytes also changed ("phagocytes" means the bulk of neutrophils with a small component of Mn, as it is observed in the blood because in this way the O₂-metabolism of blood

cells is evaluated in total) - the intracellular oxygen metabolism was significantly enhanced during phagocytosis of opsonized zymosan 24 hours ($p = 0.003$) after the surgery (Fig. 2B). It also remained increased on day seven after the surgery ($p = 0.005$). It should be noted that before the surgery, in this category of patients, there was increased production of oxygen radicals (the upper norm is 16.4 EU/10000 cells, and the value was 18.0 EU/10000 cells in the patients).

For the first time, a small increase in neutrophils with CD40 receptor expression was found in patients after CABS after the surgery. However, they significantly increased on day 7 in the postoperative period ($p = 0.009$). This observation demonstrates the activity of neutrophils and their readiness to participate in the adaptive type immune reaction, and, probably, increased production of α-TNF with cells [5, 6].

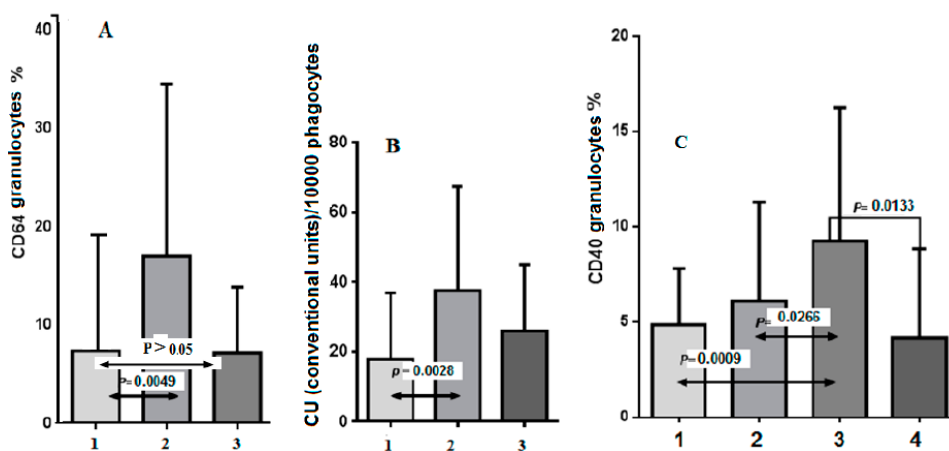


Figure 2: An increase in the number of neutrophils with CD64 (A) and CD40 (C) markers expression and the production of active oxygen radicals by phagocytes (B - shown in equivalent units per 10⁴ cells) in patients after CABS under CPB.

1 - before surgery, 2 - 1 day after the surgery, 3-7 days after the surgery, 4 - patients are receiving Immunovenin.

Unexpected results were found when analyzing the expression on neutrophils of the low affinity Fc_γ-RIII receptor (CD16+ killer K-cells of neutrophils) in patients after CABS under CPB, whose role is to form the «IgG+antigen» complex with its subsequent absorption by phagocytes, as well as the destruction of damaged IgG-bearing cells since it is also associated with the cytotoxic properties of a cell. We established the CD16 marker expression defect on neutrophils (Fig. 3). When studying the CD16 expression on neutrophils in patients on days 1 and 7 after the surgery, we established its significant change. So, in Figure 3 it can be seen that one day after the surgery, the histogram profile reflecting the affinity of Fc-gamma RIII-receptors significantly changes on the phagocytes compared to the preoperative level and remains "inferior" on the 7th day, which in some cases can contribute to the bacterial infection spreading. The significance of the discovered phenomenon for anti-infective organism protection has

not yet been determined, but most likely, it is still negative. It should be noted that this phenomenon is not described in the literature.

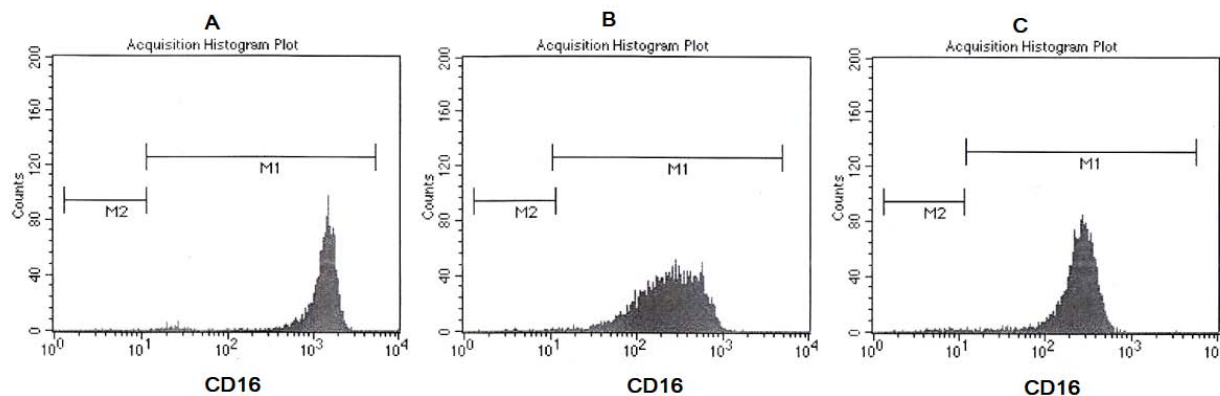


Figure 3: Neutrophilic CD16 marker expression change in patients after CABS under CPB.

A-before surgery; B- 1 day after the surgery; C- 7 days after the surgery.

It should be noted that in some cases, the expression of CD35 marker (CR1 complement immunoadhesin receptor) in patients after CABS under CPB also changed. However, this phenomenon was not

observed in all patients, a y nine from 53 (19,68%), compared to the expression of CD16 marker, which was constantly changing in all 53 the operated patients (Fig. 4).

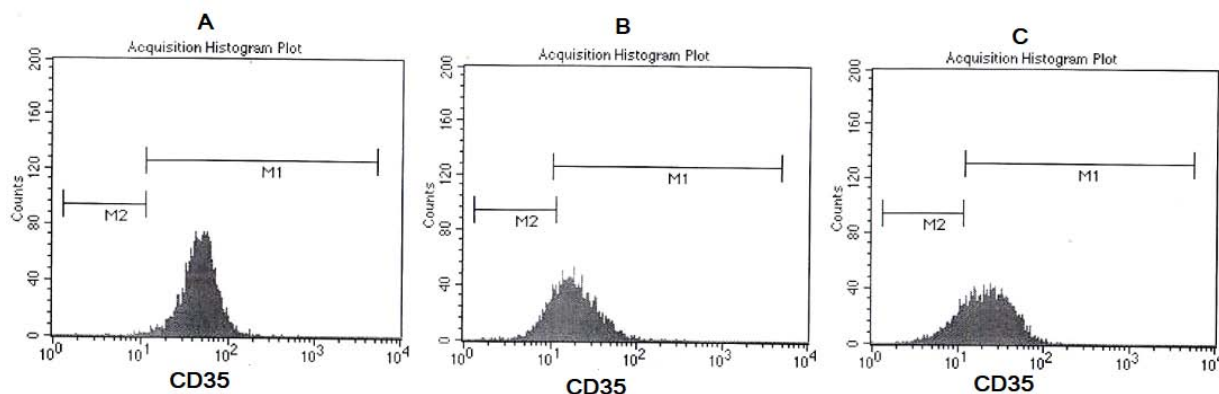


Figure 4: CD35 (CR1-complement receptor) expression change on neutrophils in patients after CABS under CPB.

A-before surgery; B- 1 day after the surgery; C- 7 days after the surgery.

Monocytes are the second most important and functional active innate immunity cells, although their number in circulation is much less than that of neutrophils (from 7 to 10%). Their significance in cardiovascular pathology is confirmed by numerous studies. Monocytes, like neutrophils, participate both in "positive" reactions and in "negative" ones in case of a cardiopathy. In this work, it is clearly shown that in patients after CABS under CPB, there is a change in the number of monocytes with the expression of membrane antigens. Figure 5A shows a significant increase in the number of monocytes with CD16 membrane marker (low-affinity Fcγ -RIII) expression one day after the surgery with normalization by day seven and a significant decrease in HLA-DR+ monocytes, returned to a normal value on day 7 (Fig. 5C).

On the other hand, CD56+ monocytes sharply increased immediately after the surgery, but also normalized on day 7 (Fig. 5D). Most likely, these dynamics are due to surgical intervention and a

developed inflammatory response. In any case, a decrease in the number of HLA-DR+ monocytes and an increase in CD56+ monocytes reflects particularly the inflammation development [29,34,35].

For the first time, we conducted a study of the CD4 monocytes content in patients after CABS under CPB. It showed a significant decrease in cells on the first day and seven days after the surgery (Fig. 5B). Unfortunately, little work has been devoted to the study of CD4 monocytes, and their role in immune regulation has not been studied. However, interesting studies on the role of CD4 monocytes are provided in [29]. Thus, it was shown that activation of the CD4 marker on cells through interaction with the major class II histocompatibility complex (MHC-II) triggers the production of cytokines and the differentiation of monocytes into functionally mature macrophages. Therefore, we can assume that the decrease in CD4 monocytes content that we observed in patients after CABS under CPB is a negative factor.

Therefore, HLA-DR and CD4 membrane molecules can be apparently and fairly attributed to stress markers of monocytes. To a certain extent, this is

confirmed by developed similar cellular changes in aseptic conditions of the postoperative period.

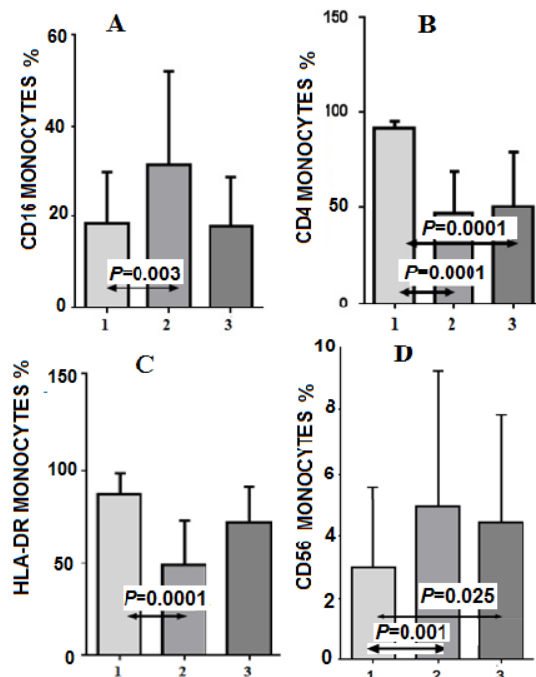


Figure 5: Change in monocytes content with the expression of CD16 marker (A), CD4 (B), HLA-DR+ antigens (C), and CD56 marker (D) in patients after CABS under CPB.

1 - before surgery, 2 – 1 day after the surgery, 3 -7 days after the surgery.

The revealed increase in the content of killer monocyte cells having expressed Fcγ receptors III (CD16+) [Fig. 5A] also possibly reflects an increase in the bactericidal properties of monocytes and their enhanced destruction of damaged cells immediately after the surgery with complete restoration of their function by day 7 of the postoperative period.

A study of natural killer effectors (CD56+CD16+ NK-effectors) belonging to the cells of innate immunity, demonstrated their increase in patients on day one after the surgery (Fig. 6). So, before the surgery, the relative content of CD56+CD16+ NK-effectors was $13.0 \pm 1.2\%$, and after 24 hours after the surgery, the relative content was $17.0 \pm 1.3\%$ ($p=0.038$). This fact can be considered as positive, since natural killers of this type participate in many protective reactions of the body, including controlling cytodifferentiation, contributing to wound healing, and killing tumor cells. On the 7th day after the surgery, the relative number of these cells sharply decreased compared to the preoperative level ($p=0.0001$), which already indicates the negative functional state of natural killer effectors, which might persist after discharging the patient, indicating negative changes in the cell killer system.

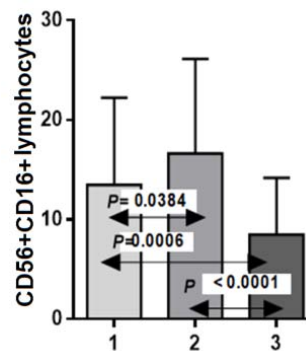


Figure 6: Change in the relative content of natural killer effectors CD56+CD16+ (%).

1 - before surgery, 2 – 1 days after the surgery, 3 -7 days after the surgery.

c) *Dynamic analysis of adaptive immunity cell changes in patients with CABG and IR*

This section provides the results of studies of lymphoid cell membrane antigens related to adaptive immunity. Fig. 7 (A-C) indicates that, after a day in the surgery site, the content of total lymphocytes and their subpopulations (CD4-T-helpers/inducers, CD8-cytotoxic/suppressor T-lymphocytes, and CD3-common T-cells).

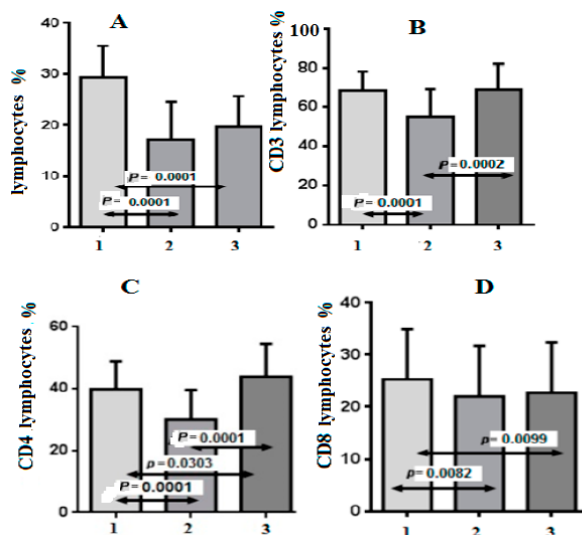


Figure 7: Changes in the relative content of total lymphocytes (A) and T-cells (B), T-helpers (C), and cytotoxic T-lymphocytes (D) in patients after CABS under CPB.

1 - before surgery, 2 – 1 days after the surgery, 3 -7 days after the surgery.

Underwent severe suppression, which most likely reflects their response to surgical trauma. By the time when patients were discharged (mostly, on day 7), the pattern was, however, different. A deep decrease in the content of total lymphocytes (7A) and cytotoxic/suppressor T-lymphocytes (7D) was noted up to the day of discharge and, possibly, continued further; this is an undoubtedly negative factor regarding the alleged subsequent development of clinical immunodeficiency. At the same time, an increase ($p=0.03$) of T-helper/regulatory lymphocytes by day seven may be a compensatory reaction of the immune system in response to CD8 T-lymphocytes suppression. In any case, this justifies a required examination of the patients that underwent surgery even after they are discharged with any possible complications stated.

Thus, the situation is traced in which specific lymphoid populations respond differently to stressful conditions caused by the surgery, that must be taken into account in cardiac surgery practice regarding CABS under CPB.

The purely opposite (compared to T-cells) change in the population of B-cells during heart surgery is noteworthy: on the first day, there was its significant increase ($p=0.0001$; Fig. 8A) with recovery occurred on day 7.

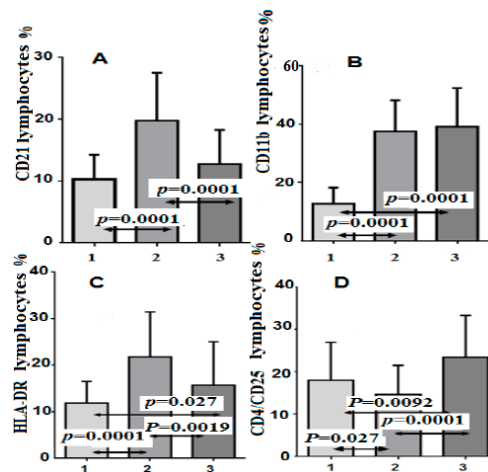


Figure 8: Changes in the relative content of B-lymphocytes (A), lymphocytes with the expression of integrin molecules LFA-1 (B), HLA-DR+ antigens (C), and T-regulators (D).

1 - before surgery, 2 – 1 day after the surgery, 3 -7 days after the surgery.

This phenomenon can be explained by the possible release into the peripheral blood of the so-called B-regulatory lymphocytes, which by producing IL-10, contribute to significant suppression of the inflammatory process [23,30], which in this case can be observed during the surgical intervention.

An increase in the relative content of CD11b lymphocytes with the expression of cell adhesion and migration receptors (LFA-1 integrins), phagocytosis of bacteria and particles opsonized by the complement component C3bi [31], (Fig. 8B) on day one и 7 ($p=0.0001$) after the surgery was established. At the same time, an increase in % of lymphocytes with HLA-DR+ antigen expressed (Fig. 8-2C, $p=0.0001$ and 8-3C,

$p=0.027$) was noted. In this regard, it is important that the function of HLA-DR antigens means participation in the presentation of antigens to T-cells during the immune response development to various pathogens and non-infectious antigens. It should be noted (Fig. 8D) that the count of T-regulatory lymphocytes significantly increased ($CD4+CD25+$, $p=0.009$) by the time when patients were discharged; it can presumably reflect a decrease in the hyperactivation of the immune system, which begins on day 7, after the presumably rapid development of the postoperative autoimmune process ($CD4+CD25+$ deficiency, $p=0.027$).

Therefore, during CABS under CPB, both innate and adaptive immunity are activated, which should be taken into account in the selection of immunomodulatory drugs.

d) *Analysis of immunity activation indices in patients with CABS under CPB*

The section includes a study of activation indices reflecting the state of immunity in patients after CABS under CPB. The data provided in Fig. 9A indicates that the average value for the group of patients with the LII index (leukocyte intoxication index) most effectively reflects the state of endogenous intoxication of the body, which was high, which is determined by a special calculation formula using the patients' peripheral blood cells [32]. Its value increased in all time points in the postoperative period ($p=0.0001$ and $p=0.02$).

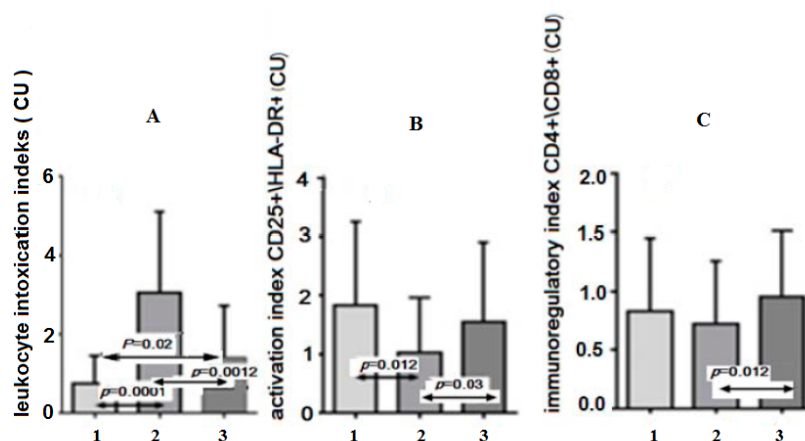


Figure 9: Activation indices change in patients after CABS under CPB.

A - LII (CU); B - $CD25+/HLA-DR+$ (CU); C - immunoregulatory $CD4+/CD8+$ (CU).

1 - before surgery, 2 - 1 day after the surgery, 3-7 days after the surgery.

A dynamic analysis of the activation indices $CD25+/HLA-DR+$ showed a significant decrease in the parameter ($p=0.012$) on the first day after the surgery (Fig. 9B), followed by recovery on the 7th day after the surgery. The stated index is very significant because it reflects the development of the depletion of the functional reserve of the immune response [40]. We can consider that its normalization on the 7th day after the surgery should be regarded as a positive phenomenon. At the same time, changes in the immunoregulatory index $CD4+/CD8+$, which reflect a severe inflammatory process with its values well below 1.0, did not reveal any significant changes on the 1st and 7th day after the surgery compared to the preoperative period (Fig. 9C), which most likely indicates severe and more local inflammation after CABS under CPB. Nevertheless, all the detected changes once again confirm the significant role of adaptive immunity in CABS operations under CPB.

e) *Analysis of humoral immunity factors (immunoglobulins) in patients after CABS under CPB*

Since immunoglobulins IgG, IgM and IgA determine the protection of the human body from various pathogens (bacteria, viruses, and other foreign substances), their determination in the serum of patients after CABS under CPB is a medical necessity. Fig. 10 shows the quantitative content of IgG, IgM, and IgA (g/L) in the serum of patients before the surgery and on days 1 and 7 after it.

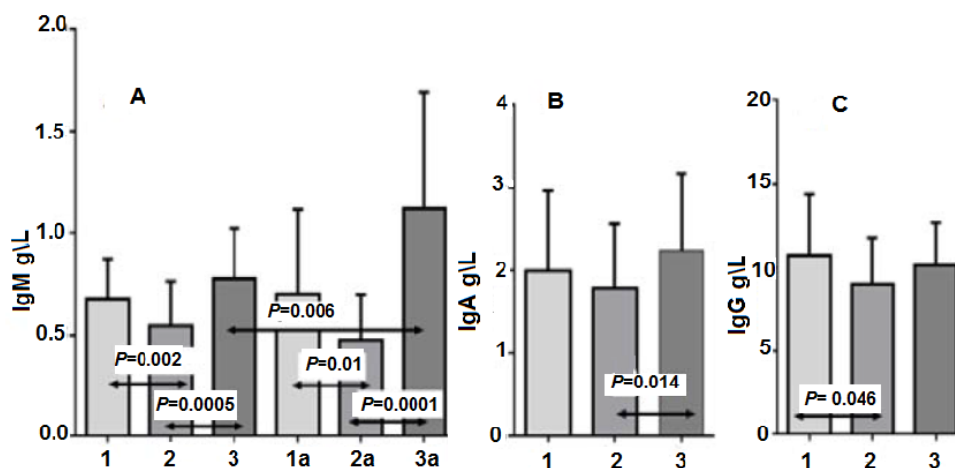


Figure 10: The average absolute content (g/L) of IgG (A), IgA (B), and IgM (C) immunoglobulins in blood serum in patients after CABS under CPB.

1 - before surgery, 2 - 1 day after the surgery, 3-7 days after the surgery, 1a - 2a - 3a - patients receiving Immunovenin.

As it turned out, a significant decrease of an average level of immunoglobulins in patients on the 1st and normalization on day seven after the surgery concerned only IgG and IgM classes, whereas the change in IgA level was not reliable (Fig. 10B). The most significant drop in concentration ($p=0.002$) was observed in IgM immunoglobulin, the most important key immunoglobulin, since it is firstly produced by the body in response to the introduction of a pathogen and has a significantly higher valency and avidity compared to IgG. Positive is the fact that IgM and IgG levels are completely restored (only by average values of protein levels for a group of patients!) by the time when patients are to be discharged.

f) *The use of the officinal IgG preparation (Immunovenin) in patients with CABS under CPB*

It is very important to note that the studies performed (see above) resulted in serious negative changes revealed in the state of the immune system in patients having undergone CABS under CPB; the changes predominantly persisted at the time of their discharge. These include severe leukocytosis, granulocytosis, and monocytosis, a sharp increase in stab neutrophils, oxidative stress of phagocytes, and endogenous intoxication. Negative changes also affected the adaptive immunity and manifested as a natural killer deficiency, lymphocytes, cytotoxic/suppressor T-cells, and other disorders. Therefore, for immunocorrection, studies were performed with a small number of patients involved ($n = 18$) and concerned the officinal powerful IgG immunotropic drug, i. e. Immunovenin, that, according to our previously obtained data on gabriglobin (Immunovenin analog), levels many of the above immune parameters in patients (42, 43).

It turned out that the administration of Immunovenin was characterized by a significant effect exerted mainly on indicators of innate immunity state in patients. So, once Immunovenin was administered, the

content of leukocytes, granulocytes, and monocytes by day 7 was significantly (and reliably) lower than that in patients not receiving the drug (Fig. 1A, B, D).

It is of importance that the application of Immunovenin resulted in the number of stab neutrophils reaching the preoperative level on day 7 (Fig. 1C, values in 1a and 3a charts, $p=0.07$), while in the group without receiving Immunovenin their content remained significantly increased (with the differences remaining highly significant, $p=0.0001$). No similar result was found when determining the content of granulocytes and monocytes.

The number of stab neutrophils reduced back to normal is a positive prognostic sign since an increase, and prolonged circulation of this cell type in the bloodstream is considered an unfavorable sign. It is associated with impaired cardiac activity [27]. Of similar importance are decreased markers of the inflammatory process in patient's body (total leukocytes, granulocytes, and monocytes, respectively $P=0.008$; $=0.006$; $=0.02$; Fig. 1A, B, D), which indicates a significant decrease in the intensity of the inflammatory process in patients than underwent CABS under CPB and were treated with an immune preparation. This observation can be considered fundamental for the corrective immunotropic therapy given to cardio-surgical patients, including the therapy applied for their rehabilitation.

In patients receiving Immunovenin, on the 7th day after the surgery, the number of cells with CD40 membrane expression significantly decreased ($p=0.013$) compared to the untreated patients (Fig. 2C, group 4). Such a reaction of cells also can reflect the positive effect of immunoglobulin on the course of the inflammatory process after the surgery.

We calculated the relative number of patients with increased LII (>1.5 UE) in the groups which received the immunoglobulin G preparation

(Immunovenin) and did not receive the same (Fig. 11). It turned out that after the administration of the drug to patients, their number decreased much more than those who did not receive the drug, and the difference turned out to be highly reliable ($\chi^2 = 30.57, p < 0.002$).

Therefore, the administration of Immunovenin after CABS under CPB is accompanied by a significant decrease in the endogenous intoxication of the body, which is of great importance for maintaining the health of the operated patients.

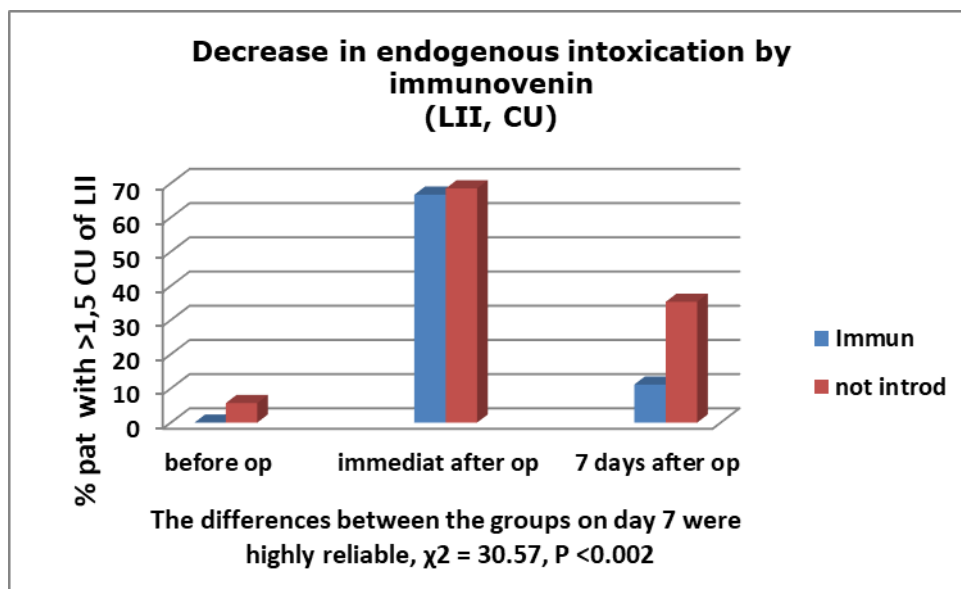


Figure 11: Decrease in endogenous intoxication (LII-conventional units-CU) in patients after CABS under CPB who received immunosuppression therapy with Immunovenin (IgG preparation).

Designations: op - operation, Immune - Immunovenin, not introd - not administered, immediate - immediately after the surgery, pat - patients

Finally, a significant increase was revealed in the IgM norm in the group of patients receiving Immunovenin (Fig. 10.3a, $p = 0.006$), which may be a compensatory immunotropic-related reaction after a pronounced protein deficiency developed immediately after the surgery.

However, immuno-replacement therapy with Immunovenin in the case of IgG deficiency in patients after CABS under CPB did not have a significant effect on eliminating its deficiency, since it returned to normal by the 7th day in the group under conventional treatment when calculating the average protein content. Moreover, when calculating the number of patients with IgG deficiency on the 7th day of the postoperative period according to the χ^2 criterion, there was no significant difference in the groups treated with and without Immunovenin ($\chi^2 = 1.19, p > 0.05$). However, the positive effect of Immunovenin in patients after CABS under CPB in the number of patients with IgG deficiency nevertheless was observed, since, on the 1st day of the postoperative period, the deficiency was detected in 60% of patients. After the application of Immunovenin, their number decreased to 6.67%. *I.e.*, it decreased nine times, while in the group without Immunovenin, the number of patients with IgG deficiency in the same period remained the same: 22.2%. Therefore, we can conclude that with such changes in the blood immunoglobulins of patients as a result of surgery,

Immunovenin should be administered during CABS under CPB. Moreover, it should be administered probably even before the surgery, which will help stabilize their concentration in the bloodstream during the surgery. However, of course, this possibility requires experimental confirmation and more extensive clinical material.

To judge how Immunovenin affects the adaptive immunity state in patients after CABS under CPB, the obtained data were insufficient, and therefore further studies are required in the long run.

IV. GENERAL DISCUSSION

A significant role in the heart pathology is firmly established to be attributed to the innate immunity cells, *i.e.*, neutrophils and monocytes [1,3,34,35]. During heart surgery, the activation of this cell link is registered, which is well shown with laboratory tests. Thus, within this study, we found that neutrophils and monocytes are subject to the greatest quantitative and qualitative changes when performing surgical interventions on the heart. If, on day seven, after the surgical intervention, the features of adaptive immunity cells return to normal, the functions of neutrophils and monocytes at this time are still far from the preoperative values. This observation is extremely important as similar changes in the immune status can later turn out to be pathologically altered in

some of the discharged patients and be accompanied by several serious complications. Regarding this possibility, the discharged patients are to be monitored for several months, initially, by filling out a special questionnaire to identify various complications in patients having undergone the surgery. In the future, it will become clear what needs to be done to prevent them.

During the study, for the first time we were able at a heart surgery to establish quantitative and functional changes in key cells of the innate immunity with expression in the neutrophils of CD64, CD16, and CD40 membrane markers, and in monocytes, *i.e.*, CD4, CD16, CD56, and HLA-DR. The mentioned cell markers are actively involved at various stages of the body's immune defense and reflect its features before the surgery and on day one and day seven after it. So, though it was previously considered that the high-affinity Fc γ -I receptor (CD64) or the neutrophils, carrying it, increased mainly during the infectious process or sepsis, it turned out that such processes occurred with neutrophils in patients having undergone CABS under CPB. Since the inflammatory process caused by surgery usually occurs under aseptic conditions, we can assume that CD64 neutrophil membrane marker should be classified less as a "septic" marker, more as a stress-induced antigen. This observation is undoubtedly fundamental and will contribute to the development of new directions in immunotropic therapy regarding clinical immunology in patients having undergone heart surgery. Nevertheless, against the background of an infectious process, especially a severe one, the CD64+ marker is certainly still a "septic" marker of pathology, which we clearly showed [36,37].

Similar considerations should be applied to neutrophil CD16 receptors, HLA-DR, and monocyte CD16 receptors, the changes in expression of which depend significantly on a result of the surgery.

For the first time, we also found an increase in the content of CD40+ neutrophils. It was observed on the first day after the surgery and then increased significantly on day 7. This phenomenon can be interpreted as a positive one since neutrophils are known to actively participate in the immune response [6,7] and thrombolysis [38]. This phenomenon can also cause a negative effect because binding to the CD40 ligand can cause negative processes within the body [39]. Since the CD40 receptor is the 5th member of the TNFRSF5 receptor superfamily, it is possible that excess TNF levels can be increased [40]. In patients having undergone CABS, Immunovenin administered on day 1 of the postoperative period had the dramatic importance for the correction of the innate immunity. In this case, there was a significant decrease in the number of neutrophils (the stab neutrophil population reached normal values as compared to patients not receiving the

drug). A significant decrease in monocytes was also observed on day seven after the intervention. The results obtained indicate that the drug has anti-inflammatory properties. In domestic and foreign literature, no such approach is found. It must be noted that since several patients had pre-operative neutrophil activity due to the oxygen radicals production and CD40 expression, it may be advisable to administer Immunovenin to patients in the post-operational period. Here, we must add that 15% of the patients having undergone a surgical intervention had an IgG blood deficiency, and 33% of them had an IgM deficiency. Interesting and, in a certain sense, positive data were obtained regarding the calculated dynamics in the number of patients suffering from IgG deficiency who received Immunovenin injection as compared to the group not having to receive the drug; the deficiency was not detected when determining the average content of immunoglobulins in the corresponding groups of patients. Following this processing of results, the decrease in the number of patients suffering from IgG deficiency was much lower in the drug infusion group than that in the group of patients not having received Immunovenin. Once administered to patients, Immunovenin significantly increased IgM in them on day 7 of the postoperative period. This is a positive fact, and it most likely reflects the compensatory reaction of the humoral immune link, since IgM provides early protection of the body from bacterial agents. In patients having undergone surgery and not having received the drug, no significant increase in IgM was detected.

Adaptive immunity cells are also subject to change during heart surgery. So, studies [21,24] show that the functional ability of the T-cell link changes significantly during cardiac surgery, while the response to PPD (Tuberculin PPD - Purified Protein Derivative) is thus reduced. In [41], a decrease in the relative content of CD3+ lymphocytes by 9.0% and an increase in the level of CD8+ by 1.2 times were recorded, with an absolute and relative number of B-cells increased by 1.9 and 2.3 times, respectively. Another observation [24], also associated with the CABS surgery, indicated a decrease in the number of T-lymphocytes (T-helpers). In contrast, the number of suppressors/cytotoxic T-cells and B-cells in the studied blood samples was free of any changes. When comparing the cited data and the immune findings that we obtained, the work performed at our Center revealed a significant increase in natural killer cells on day 1 of the postoperative period and a decrease in the number of total CD3, CD4 (helpers/inducers), and CD8 (cytotoxic/suppressors) lymphocytes, together with an increase in the number of CD21+ B-lymphocytes. This sharp decrease in total lymphocytes and cytotoxic/suppressor T-cells after discharge may be complicated by the developed immunodeficiency. At the same time, the increase in T-helper lymphocytes (detected on day 7) probably

occurred due to the compensatory reaction of the immune system due to a deep deficiency of this type of cells on day 1 of the postoperative period, with a simultaneous deficit noted throughout the postoperative period of CD8+ T lymphocytes.

At the same time, on day 1 of the postoperative period, not only the number of B-lymphocytes and lymphocytes with the expression of LFA-1 (CD11b+) and HLA-DR+ lymphocyte integrin molecules increased, but also the content of HLA-DR+ lymphocytes and T-regulatory cells (CD4+CD25+) increased on day 7 of the postoperative period. Immediately after the surgery, such changes in adaptive immunity cells could reflect the release of the so-called regulatory B-lymphocytes into circulation and their release of anti-inflammatory IL-10, possibly reducing the intensity of the developing inflammation. The accumulation of lymphocytes with enhanced migration activity is also possible. Moreover, the preservation of an increased number of HLA-DR+ and CD4+CD25+ lymphocytes on day seven could speak of an increased presentation of antigens by lymphocytes and, at the same time, a decrease in the hyperactivation of the immune system that occurs shortly after the surgery. Naturally, these speculations should be proved in further studies, since they are of fundamental importance in cardiac surgery (CABS under CPB).

V. CONCLUSION

In heart surgery (CABS under CPB), most of the innate and adaptive immunity indicators change significantly. The use of Immunovenin positively affects the innate immunity state. Thus, there is a potential opportunity to apply immunoglobulin preparations to relieve the acute phase in the postoperative period by activating innate immune cells for cardiac surgery and also for other surgical interventions. Further, it is planned to conduct fundamental research on this phenomenon using modern surgical technologies.

REFERENCES RÉFÉRENCES REFERENCIAS

1. Frantz, S., Falcao-Pires, I., Balligand, J. L., Bauersachs, J., Brutsaert, D. et al. 2018. The innate immune system in chronic cardiomyopathy: A European Society of Cardiology (ESC) scientific statement from the Working Group on Myocardial Function of the ESC. *Eur J Heart Fail*, 20: 445-459.
2. Zhang, Y., Bauersachs, J., Langer, H.F. 2017. Immune mechanisms in heart failure. *Eur J Heart Fail*, 19: 1379-1389.
3. Mann, D.L. 2015. Innate Immunity and the Failing Heart. *The Cytokine Hypothesis Revisited. Circ Res*, 116: 1254-1268.
4. On, Y., Taylor, J.M., Bannon, P.C.I., Geczy, C., Kritharides, L. 2005. Circulating CD10-/CD16 low neutrophils provide a quantitative index of active

- bone marrow neutrophil release. *Br J Haematol*, 13(1): 508-19.
5. Buckley, C.D., Ross, E.A., McGettrick, H.M., Osborne, C.E., Haworth, O.K. et al. 2006. Identification of a phenotypically and functionally distinct population of long-lived neutrophils in a model of reverse endothelial migration. *J Leuko Bio*, 792: 303-11.9.
6. Davis, R.E., Sharma, S., Conceição, J., Carneiro, P., Novais, F. et al. 2017. Phenotypic and functional characteristics of HLA-DR+ neutrophils in Brazilians with cutaneous leishmaniasis. *J Leukoc Biol*, 101: 739-749.
7. Cai, S., Kandasamy, Rahmat, J.N., Tham, S.M, Bay, B.H. et al. 2016. *Lactobacillus rhamnosus*. GG activation of dendritic cells and neutrophils depends on the dose and time of exposure. *J Immunol Res*, 2016: 8.
8. Horckmans, M., Ring, L., Duchene, J., Santovito, D., Schloss S. et al. 2017. Neutrophils orchestrate post-myocardial infarction healing by polarizing macrophages towards a reparative phenotype. *Eur Heart J*, 38: 187-197.
9. Vono, M., Lin, A., Norrby-Teglund, A., Koup, R.A., Liang, F., Loré, K. 2017. Neutrophils acquire antigen presentation capacity to memory CD4+ T cells in vitro and ex vivo. *Blood*, 129: 1991-2001.
10. Araújo, H.A., Franck, G., Shvartz, E., Sukhova, G., Libby, P. 2015. TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion. *Eur Heart J*, 36:1394–1404.
11. Hoyer, F.F., Nahrendorf, M. 2017. Neutrophil contributions to ischaemic heart disease. *European Heart Journal*, 38: 465–472.
12. Merino, A., Buendia, P.A., Martin-Malo, A.F. et al. 2010. Senescent CD14+CD16+ monocytes exhibit proinflammatory and proatherosclerotic activity. *J Immunol*, 186: 1809–1815.
13. Weber, C, Shantsila, E., Hristov, M., Caligiuri, G., Guzik, T. et al. 2016. Role and analysis of monocyte subsets in cardiovascular disease Joint consensus document of the European Society of Cardiology (ESC) Working Groups “Atherosclerosis & Vascular Biology” and “Thrombosis”. *Thromb Haemost*, 116: 626–637.
14. Shahid, F., Lip, G.Y., Shantsila, E. 2018. Role of monocytes in heart failure and atrial fibrillation. *J Am Heart Assoc*, 7: 167-304.
15. Wrigley, B.J., Shantsila, E., Tapp, L.D., Lip, G.Y. 2013. CD14+ +CD16+ monocytes in patients with acute ischaemic heart failure. *Eur J Clin Invest*, 43: 121-130.
16. Suzuki, A., Fukuzawa, K., Yamashita, T., Yoshida, A., Sasaki S. et al. 2017. Circulating intermediate CD14+ +CD16+ monocytes are increased in patients with atrial fibrillation and reflect the

- functional remodelling of the left atrium. *Europace*, 19: 40-47.
17. Tapp, L.D., Wrigley, B.J., Pamukcu, B., Lip, G.Y. 2012. The CD14++CD16+ monocyte subset and monocyte-platelet interactions in patients with ST-elevation myocardial infarction. *J Thromb Haemost*, 10: 1231-41.
 18. Rothe, G., Gabriel, H., Kovacs, E., Klucken, J., Stöhr, J., Kindermann, W., Schmitz, G. 1996. Peripheral blood mononuclear phagocyte subpopulations as cellular markers in hypercholesterolemia. *Arterioscler Thromb Vasc Bio*, 16: 1437- 1447.
 19. Kazimierczyk, E., Eljaszewicz, A., Zembko, P., Tarasiuk, E., Malgorzata, M. et al. 2019. The relationships among monocyte subsets, miRNAs and inflammatory cytokines in patients with acute myocardial infarction. *Pharmacological Reports*, 71: 73-81.
 20. Patel, A.A., Zhang, Y., Fullerton, J.N., Boelen, L., Rongvaux, A.S. et al. 2017. The fate and lifespan of human monocyte subsets in steady state and systemic inflammation. *J Exp Med*, 214: 1913-1923.
 21. Sano, T., Morita, S., Tominaga, R., Masuda, M., Tomita, Y., Yasutsune, T., Yasu, H. 2002. Adaptive immunity is severely impaired by open-heart surgery. *Jpn J Thorac Cardiovasc Surg*, 50: 201-205.
 22. Zhu, Z.F., Meng, K., Zhong, Y.C., Qi, L., Mao, X.B. et al. 2014. Impaired circulating CD4+LAP+ regulatory T cells in patients with acute coronary syndrome and its mechanistic study. *PLoS One*, 9.
 23. Jiao, J., Lu, Y-Z., Xia, Ni., Wang, Y-Q., Tang, T-T. et.al. 2018. Defective Circulating Regulatory B Cells in Patients with Dilated Cardiomyopathy. *Cell Physiol Biochem*, 46: 23-35.
 24. Markewits, A., Lante, W., Franke, A., Marohi, K., Kuhimann, W.D., Weinhold. C. 2001. Alterations of cell-mediated immunity following cardiac operation: clinical implication and open questions. *Shock*, 16: 10-5.
 25. Caldefie-Chezet, F., Walrand, S., Moinard, C.T., Tridon, A., Chassagne, J. et al. 2002. Is the neutrophil reactive oxygen species production measured by luminol and lucigenin chemiluminescence intra or extra cellular? Comparison with DCFH-DA flow cytometry and cytochrome c reduction. *Clin Chim Acta*, 319: 9–17.
 26. Holzer, K., Richter, A., Konietzny, P., Schübel, F., Wilhelm, K. et al. 2003. Functions of circulating and intra-abdominal polymorphonuclear leukocytes during human secondary peritonitis. *Zentralblatt fur Chirurgie*, 128: 291–297.
 27. Kong, T., Hoon Kim, T., Seok Park, Y., Phil Chung S., Sun Lee, H. et al. 2017. Usefulness of the delta neutrophil index to predict 30-day mortality in patients with ST segment elevation myocardial infarction. *Sci Rep*, 16:15718. doi: 10.1038/s41598-017-15878-5.
 28. Zhen, A., Krutzik, S.R., Levin, B.R., Kasparian, S., Zack, J.A. et al. 2014. CD4 Ligand on human blood monocytes triggers macrophage differentiation and enhances HIV infection. *J Virol*, 88. doi: 10.1128/JVI.00616-14.
 29. Zemskov, V.M., Pronko, K.N., Ionkin, D.A., Chzhao, A.V., Kozlova, M.N. et al. 2019. Immune status of pancreatic cancer patients receiving cryosurgery. *Medical Science*, 7:73. doi: 10.3390/medsci7060073.
 30. Zhou, C.J., Ma, F., Liao, W.J., Song, L.J., Yu, D. et al. 2019. Restoration of immune suppressor function of regulatory B cells collected from patients with allergic rhinitis with Chinese medical formula Yupingfeng San. *Am J Transl Res*, 11: 1635-1643.
 31. Lukácsip, S., Nagy-Baló, Z., Erdei, A., Bajtay, Z. 2017. The role of CR3 (CD11b/CD18) and CR4 (CD11c/CD18) in complement-mediated phagocytosis and podosome formation by human phagocytes. *Immunol Lett*, 189: 64-72.
 32. Kalf-Caliph, Y.Y. 1941. Leukocyte index of intoxication and its practical significance. *Medical business*, 1: 31-35.
 33. Tarasyuk, V.V., Titov, L.P., Zhmurovskaya, L.S. 2005. Methods of diagnosis of cell-molecular damage to the T-system immunity in hepatitis C and mixed hepatitis B+C. Achievements of medical science of Belarus, (UDC: 616.36.-002.24:578.891] – 097), http://med.by/dmn/book.php?book=05-7_23.
 34. Yang, X.J., Zhang, L., Yu, C., Yang, X-F., Wang, H. 2014. Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases. *Biomarker Res*, 2: 2-9.
 35. Italiani, Y.P., Boraschi, D. 2014. From monocytes to M1/M2 macrophages: Phenotypical vs functional differentiation. *Frontiers in Immunol*, 5: 514. doi: 10.3389/fimmu.2014.00514.
 36. Zemskov, V.M., Alekseev, A.A., Kozlova, M.N., Shishkina, N.S., Gnatenko, D.A. et al. 2016. Immune diagnostics of septic complications in burns. *Biology Bulletin Reviews*, 6: 344–354.
 37. Zemskov, V.M., Alekseev, A.A., Kozlova, M.N., Shishkina, N.S., Gnatenko, D.A et al. 2016. A composite biomarker panel as a highly informative and reliable tool for predicting septic complications. *Jacobs Journal of Biomarkers*, 2: 1-10.
 38. Stief, T.W. 1991. Nonradical excited oxygen species induce selective thrombolysis in vivo. *Thromb Res*, 62:147-63.
 39. Rizvi, M., Pathak, D., Freedman, J.E., Chakrabarti. 2008. CD40-CD40 ligand interactions in oxidative stress, inflammation and vascular disease. *Trends Mol Med*, 14: 530-8.

40. Zemskov, A.M., Zemskov, V.M., Karaulov, A.V. (Ed.). 2008. The Textbook "Clinical Immunology" for students of higher vocational education. Moscow: Publishing House GEOTAR- Media, 426 p.
41. Golovkin, A.S. 2014. Mechanism of syndrome of system inflammatory response after operations with application of artificial blood circulation. The dissertation for the degree of Doctor of Medical Sciences. Kemerovo.
42. Zemskov, V.M., Alekseev, A.A., Kozlova, M.N., Shiskina, N.S., Bleykhman, D.A. et al. 2017. Changes in the immune system depending on the stage of burn disease and the area of thermal destruction. immunoglobulin replacement therapy with gabriglobin. Internat J Recent Scientific Research, 8(2), 15653-15662. DOI: <http://dx.doi.org/10.24327/ijca.2017.3404.0282>
43. Zemskov, A.M., Zemskov, V.M., Zemskova, V.A., Zolodov, V.I., Dorohov, E.V. 2017. Immunoglobulins – present and future. Internat J Current Advanced Research, 6(4), 3400-3404. DOI: <http://dx.doi.org/10.24327/ijcar.2017.3404.0282>





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Unusual Biliary Complication in the Modern Surgical Century: Bouveret's Syndrome

By Andrade Ramirez MR, Mazza Diez E, Fernandez DL, Bracco RA (FACS)
& García FW (FACS)

Abstract- Background: Bouveret's syndrome is a rare type of gallstone ileus. It consists of duodenal obstruction secondary to the passage of a stone through a fistula established between the gallbladder and the duodenum.

Case Presentation: Here in, we report the case of a 60-year-old female patient who presented dyspepsia with vomiting of solids and liquids foods in the preceding weeks. Severe dehydration and asthenia concomitant. The examination showed epigastric pain with tympanic percussion. Laboratory: mild leukocytosis and hypokalemia. MRI: an image of 34 x 56 mm endoluminal hypointense is observed in duodenum compatible with biliary lithiasis. A suspicion of a fistula between the gallbladder and the duodenum was considered.

Conclusion: Bouveret's Syndrome is rare, so the diagnosis is of exclusion. The ideal treatment is endoscopic, but if this route fails, surgery is necessary, prioritizing the mini-invasive approach.

Keywords: *bouveret's syndrome, fistula, gallstone ileus, mini-invasive approach, duodenal obstruction, enterolithotomy.*

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Unusual Biliary Complication in the Modern Surgical Century: Bouveret's Syndrome

Case Report

Andrade Ramirez MR ^α, Mazza Diez E ^σ, Fernandez DL ^ρ, Bracco RA (FACS) ^ω & García FW (FACS) [¥]

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Abbreviations: MRI: Magnetic Resonance Imaging, CT: Computed Tomography.

I. INTRODUCTION

Bouveret's syndrome, described by French physician Léon Bouveret in 1896, is a rare type of gallstone ileus.^{1,2-4}

It occurs in elderly patients and consists of duodenal obstruction secondary to the passage of a stone through a fistula between the gallbladder and the duodenum. Clinical presentation, a 60-year-old female patient who came to the consultation because she was suffering dyspepsia with vomiting of solids and liquids foods during the preceding weeks. Severe dehydration and asthenia concomitant. A physical examination showed epigastric pain on deep palpation with tympanic percussion. Laboratory tests showed mild leukocytosis and hypokalemia. An abdominal ultrasound showed a collapsed gallbladder with thickened walls.

Computed Tomography (CT) of the abdomen is the method of choice to confirm the diagnosis, with a sensitivity of 93% and a specificity of 100%. However, in 15-25% of cases, the stones appear isodense and surrounded by fluid, making them difficult to identify.⁵ Magnetic resonance imaging (MRI) is more sensitive and specific. They can recognize the site of impaction, size of the stone, identify the fistula, and provide an appropriate view of the biliary tract.⁵⁻⁸

In this clinical case, MRI showed a dilated intrahepatic bile duct, a common bile duct of 7mm, and a distended stomach. In the second duodenal portion, an image of 34 x 56 mm endoluminal hypointense showed the fistula connecting the gallbladder with the duodenum and wall thickening. (Figure 1)

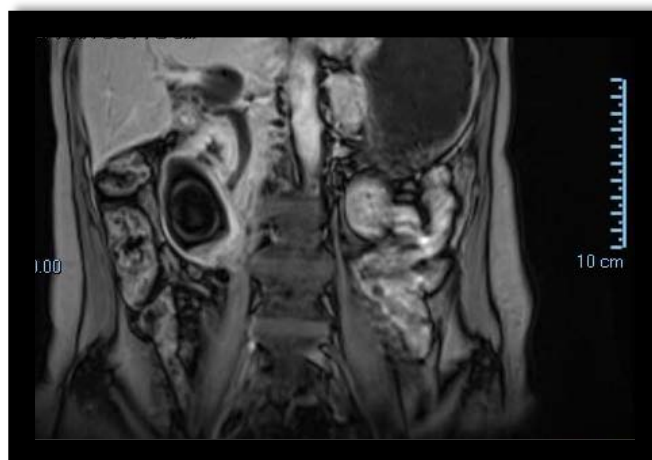


Figure 1: Endoluminal stone in second duodenal portion 34 x 56 mm. (green arrow)

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Bilioenteric fistula appears in 2-3% of cases of cholelithiasis. This communication allows the migration of the stone through the bowel, causing an intestinal obstruction (biliary ileus). Gallbladder and duodenal fistulas are the most frequent, followed by gallbladder and colon and gallbladder and stomach fistulas. Only 6% of stones associated with fistula cause obstruction because of their big size. The most common site of occlusion is the small intestine.⁹

When the stone is accommodated into the duodenum, and it obstructs the gastric emptying is called Bouveret's Syndrome, an entity that represents only 1-3% of cases of gallstone ileus.¹⁰

Complications are dehydration and gastrointestinal bleeding.^{5,9}

In the clinical case presented, endoscopic extraction was attempted, which showed a stone of 5 cm in the second duodenal portion, which was immobile and whose removal was unsuccessful. (Figure 2)

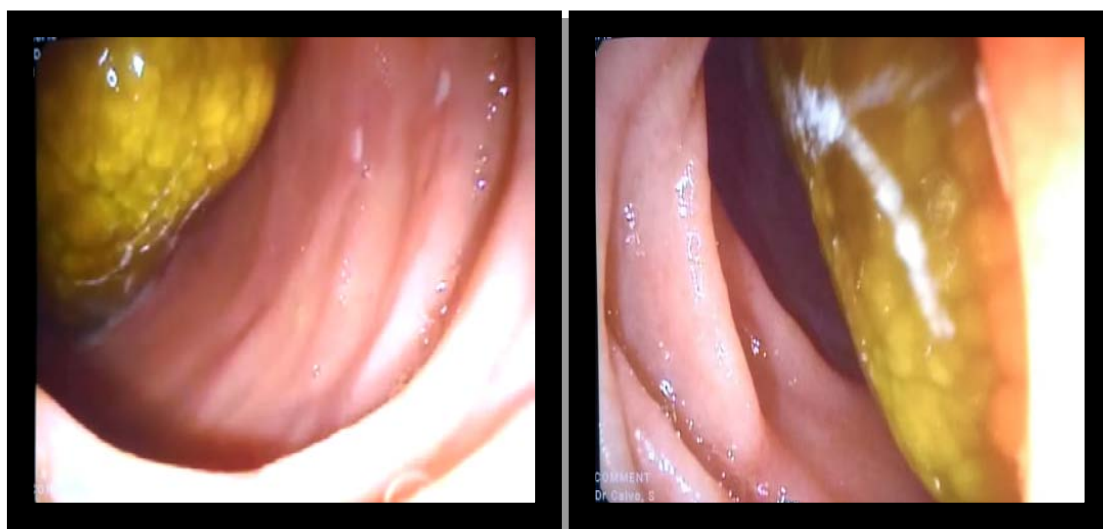


Figure 2: Endoscopic image of stone in second duodenal portion

Surgical treatment included three approaches: a) one-stage approach (by opening the small bowel and to remove the stone/gastrotomy, cholecystectomy and fistula closure), b) two-stage approach (by opening the small bowel and to remove the stone/gastrotomy and subsequent cholecystectomy and fistula closure deferred) and c) by opening the small bowel and to remove the stone/gastrotomy alone.^{2,4,5,11,12}

When the endoscopic resolution failed, we decided laparoscopic minimally invasive approach. Intraoperatively an inflammatory plastron was recognized in the right upper quadrant. Therefore, this made it difficult to visualize the gallbladder and its abnormal communication with the digestive tract. Due to the subacute inflammatory process and prioritizing the patient's safety, we decided to remove the stone by gastrotomy, leaving the treatment of the vesicular pathology and fistula for eventually the second time.

By opening the small bowel and to remove the stone / gastrotomy is less morbid. The recurrence of obstruction by a new stone is 2-5%, which mostly occurs in the first six months.¹²

Individual determinants of mortality, described as the patient's physical condition and the time delay from initial symptoms to surgery, are parameters in decision-making. Our team prioritizes the individualization of surgical treatment with the premise

"LESS IS BETTER." As we showed in this clinical case, the minimally invasive option is feasible and safe, although its use worldwide is around 10%, with conversion rates of 53%.^{4,9,10,14}

In patients with associated pathologies, in which the delay in diagnosis and age over 65 years increases morbimortality, by opening the small bowel and to remove the stone / gastrotomy alone by laparoscopy is the best option. On the other hand, in younger patients, without associated morbidities, with the good physical condition and without a long delay in diagnosis, it could opt for the resolution at a one-stage approach, which shows almost similar mortality.¹⁵

In conclusion, Bouveret's Syndrome is rare, so the diagnosis is of exclusion. The ideal treatment is endoscopic, but if this route fails, surgery is necessary, prioritizing the mini-invasive approach.

BIBLIOGRAPHY

1. Petrowsky H, Clavien P. Biliary fistula, gallstone ileus, and Mirizzi's syndrome. In: Clavien PA, Baillie J, editors. Diseases of the gallbladder and bile ducts: diagnosis and treatment. 2nd edition. Malden (MA): Blackwell Publishing; 2008; 239-51.
2. Nuño-Guzmán CM, Marín-Contreras ME, Figueroa-Sánchez M, Corona JL. Gallstone ileus, clinical

- presentation, diagnostic and treatment approach. *World J Gastrointest Surg* 2016; 8(1): 65-76.
3. Luu MB, Deziel DJ, Unusual Complications of Gallstones. *Surgical Clinics of North America* 2014; 94(2):377-394.
 4. Halabi WJ, Kang CY, Ketana N, Lafaro KJ, Nguyen VQ, Stamos MJ, Imagawa DK, Demirjian AN. Surgery for gallstone ileus: a nationwide comparison of trends and outcomes. *Ann Surg* 2014; 259: 329-335.
 5. Ploneda-Valencia CF, Gallo-Morales M, Rinchon C, Navarro-Muñiz E, Bautista-López CA, de la Cerda-Trujillo LF, Rea-Azpeitia LA, López-Lizarraga CR. El íleo biliar: una revisión de la literatura médica. *Revista de Gastroenterología de México* 2017; 82 (3): 248-254.
 6. Chang L, Chang M, Chang HM, Chang AI, Chang F. Clinical and radiological diagnosis of gallstone ileus: a mini review. *Emerg Radiol* 2018; 25(2):189-196.
 7. Chuah PS, Curtis J, Misra N, Hikmat D, Chawla S. Pictorial review: the pearls and pitfalls of the radiological manifestations of gallstone ileus. *AbdomRadiol (NY)* 2017; 42(4):1169-1175.
 8. Yu CY, Lin CC, Shyu RY, Hsieh CB, Wu HS, Tyan YS, Hwang JI, Liou CH, Chang WC, Chen CY. Value of CT in the diagnosis and management of gallstone ileus. *World J Gastroenterol* 2005; 11(14): 2142-2147.
 9. Cappell MS, Davis M. Characterization of Bouveret's syndrome: a comprehensive review of 128 cases. *Am J Gastroenterol* 2006; 101: 2139-2146.
 10. AL-Habbal Y, Ng M, Bird D, McQuillan T, AL-Khaffaf H. Uncommon presentation of a common disease - Bouveret's syndrome: A case report and systematic literature review. *World J Gastrointest Surg* 2017; 9(1): 25-36.
 11. Caldwell K M, Lee S J, Leggett P L, Bajwa K S, Mehta SS, Shah S K. Bouveret syndrome: current management strategies. *Clinical and Experimental Gastroenterology* 2018; 11: 69–75.
 12. Rabie MA, Sokker A. Cholecystolithotomy, a new approach to reduce recurrent gallstone ileus. *Acute Med Surg* 2019; 6(2):95-100.
 13. Tchercansky AN, Busnelli GL, Mihura M, Maurette RJ, "Laparoscopic Management of Bouveret's Syndrome after Failed Endoscopic Approach" *Case Reports in Surgery* 2019, Article ID 7067240, 4 pages, 2019.
 14. Tartaglia, D., Bakkar, S., Piccini, L., Bronzoni, J., Cobuccio, L., Bertolucci, A, Chiarugi, M. Less is more: an outcome assessment of patients operated for gallstone ileus without fistula treatment. *International journal of surgery case reports* 2017; 38:78–82.
 15. Mallipeddi MK, Pappas TN, Shapiro ML, Scarborough JE, Gallstone ileus: revisiting surgical outcomes using National Surgical Quality Improvement Program data. *Journal of Surgical Research* 2013; 184:84-88.



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Diastolic Dysfunction in Normotensive Patients with Diabetes Mellitus- A Double Blind Randomised Prospective Multicentre Study in North India

By Rajesh Patnaik, Vijay Verma, Man Mohan Mehra, Tushar Jain,
Vishal Nehra & Himanshu Kumar Sanju

Abstract- Aim: To study the Ventricular function of Older Patients with diabetes but without hypertension.

Type of Study: Prospective Analysis.

Methodology: 2500 Patients diagnosed as suffering from Diabetes Mellitus (either type 1 or type 2), who were normotensive but older than 18 years and visited Medicine or Cardiology Out Patient Departments in four different hospitals, were included in the study. All the patients were subjected to a detailed history and clinical examination. The mean age of patients was 48.8 yrs. 55.4 % were Males, 44.4 % were Females and, 0.2 % were not otherwise specified. Patients underwent a battery of tests including, Echocardiography.

Results: In our Study, 72 % of the patients had diabetes for a duration of less than ten years and, 28 % of the patients had more than ten years. 20% had Body Mass Index within Normal Range but Impaired in remaining 80%.

Keywords: diabetes, hypertension, echocardiography, ventricle.

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Diastolic Dysfunction in Normotensive Patients with Diabetes Mellitus- A Double Blind Randomised Prospective Multicentre Study in North India

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Results: In our Study, 72 % of the patients had diabetes for a duration of less than ten years and, 28 % of the patients had more than ten years. 20% had Body Mass Index within Normal Range but Impaired in remaining 80%. On Echocardiography, E/A ratio that is Peak velocity of early mitral flow/ Peak velocity of late mitral flow was less than 1 in 85 % of cases where as it was between 1 to 2 in the remaining 15 % of cases. IVRT that is Isovolumetric Relaxation Time was greater than 100 millisecon in 65% of cases where as it was between 60 and 100 in the remaining 35% of cases. Moreover, Deacceleration Time of E (Peak velocity of early mitral flow) was greater than 200 milliseconds in 69 % of cases, whereas it was between 150 and 200 milliseconds in the remaining 31 %.

Conclusion: Left Ventricular Diastolic Dysfunction in normotensive patients with Diabetes without evidence of coronary heart disease is higher than previously suspected especially, in North India. Conventional echocardiography is a simple, economical test for detecting Left Ventricular dysfunction in these patients.

Keywords: diabetes, hypertension, echocardiography, ventricle.

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I. INTRODUCTION

The term Diabetes mellitus which in Greek means "to run through" or "Siphon," was first coined by Arataeus of Cappadocia in 2nd century AD as a generic description for conditions causing increased urine output. Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and, protein metabolism associated with an absolute or relative deficiency in insulin secretion and insulin action, which is modulated by genetic and environmental factors resulting in micro and macroangiopathy. Important differences in the types and frequency of Diabetes mellitus and its complications have been reported between countries as well as ethnic and cultural groups.¹ Indians are genetically more susceptible to Diabetes mellitus compared to other races. India will have the largest number of diabetic subjects in the world by 2025 and one out of 5 diabetic subjects in the world will be an Indian. India is going to be the "Diabetic capital of the world".^{1,2}

Subclinical abnormalities of left ventricular function are recognized in both Type 1 and Type 2 diabetes mellitus. Studies using Doppler echocardiography have confirmed the findings of abnormal diastolic function as an early indicator of cardiac involvement in asymptomatic patients with Type 1 or Type 2 diabetes mellitus.³ The term 'diabetic cardiomyopathy' has been introduced for this condition. It has been suggested that microangiopathic lesions of the myocardium, altered composition and, fibrosis of myocardial interstitium and accumulation of lipids in myocardial cells are involved in the pathogenesis of diabetic cardiomyopathy.⁴ In 2001, Nichols et al. reported on the close link between diabetes and heart failure.⁵

II. MATERIAL AND METHODS

Our was a prospective study conducted across four centers in different states in North India. The present study was approved by the ethical committee of the Department of Cardiology, Hindu Rao Hospital, North Delhi Municipal Corporation medical college, New Delhi. 2500 Patients diagnosed as suffering from

Diabetes Mellitus (either type 1 or type 2), who, were normotensive but older than 18 years were selected randomly without awareness of both the clinician and the patient (double-blind). Diabetes was diagnosed as per ADA guidelines 2018. Patients age less than 18 years who were either Hypertensive or suffering from Congestive Heart Failure/Coronary Heart Disease or Chronic Kidney Disease or Hypo/Hyperthyroidism thyroid or Cardiomyopathy causing drugs like Donorubicin, bleomycin, adriamycin, etc.) were excluded from the study. After comprehensive history and examination, all patients underwent baseline tests like Fasting blood sugar, Post prandial blood sugar, Glycated haemoglobin, Kidney function test, Complete blood count, Chest radiograph, Electric Cardio Gram (ECG), Echocardiography, Urine routine and microscopy, Urine sugar and ketones. Also, Tread Mill Test (TMT), Thyroid profile, and Lipid profile were done in indicated cases. Echocardiography gives a detailed picture of diastolic dysfunction. The study was conducted in accordance with "Recommendations guiding physicians in biomedical research involving human subjects," adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964.

a) *2D echocardiography*

M-mode, and color Doppler examination were done by Agilent Image Point machine with 2.5 to 5 MHz probes. All recordings were done with patients in supine and left lateral position. The transducer was placed in the left parasternal, apical, and subcostal areas of the chest, and the parasternal long axis and short axis were taken to record various dimensions and measurements.

b) *Echocardiographic Measurements*

Diastolic function of the left ventricle is best assessed by evaluating the mitral inflow velocity curves (MIVC) by Echo-Doppler techniques. In this study, the following parameters were considered to evaluate LV diastolic dysfunction.

- a) Mitral 'E' velocity (Peak velocity of early mitral flow)
- b) Mitral 'A' velocity (Peak velocity of late (atrial) mitral flow)
- c) Mitral E/A ratio (Normal 1-2)
- d) Isovolumic relaxation time (IVRT) (Normal 60-100 msec)
- e) Deceleration time of mitral 'E' curve (DT of E) (Normal 150-200 msec). Mitral flow velocities were measured by pulsed wave Doppler with sample volume placed between the leaflet tips. It is necessary to keep it between the leaflet tips as Doppler parameters are dependent on the sample volume location.

III. RESULTS

2500 Patients were analyzed and compared on various parameters. Figure 1 shows the demographics of the patients involved in the study. 55.4 % were Males, 44.4 % were Females, and 0.2 % were not otherwise specified. The mean age of patients was 48.8yrs.

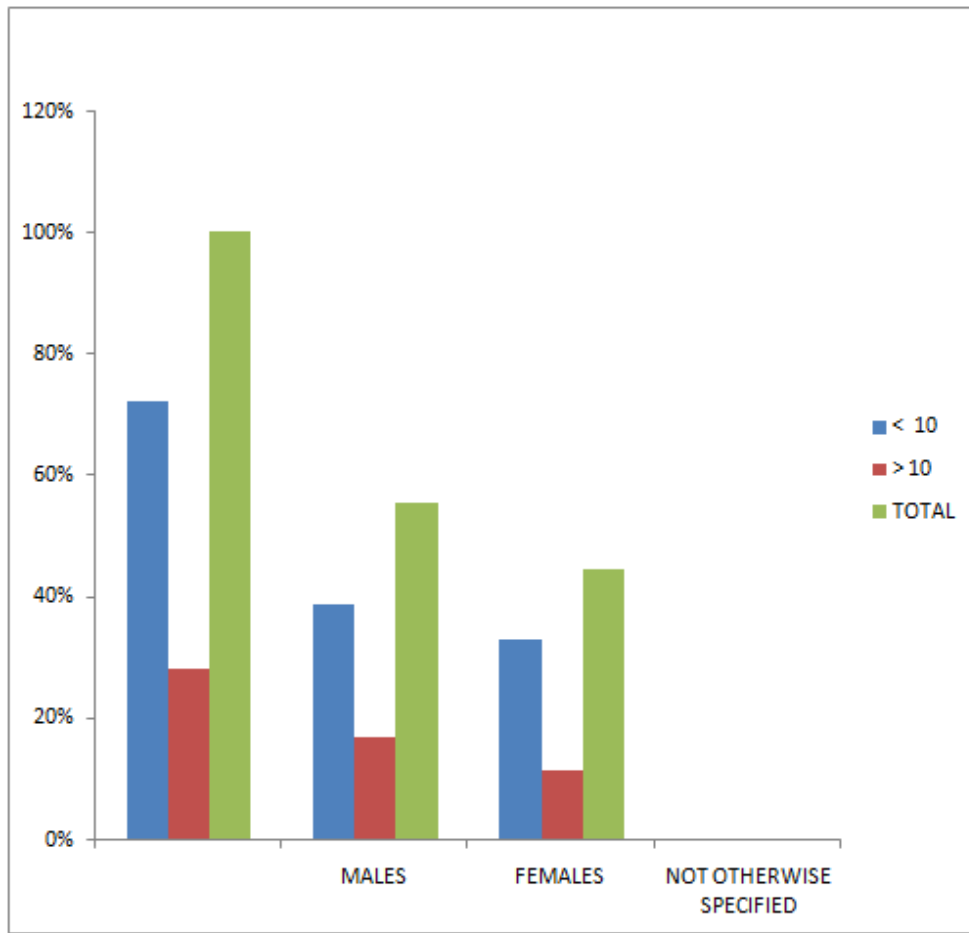


Figure 1: Gender wise distribution of patients

The majority of the patients belong to the duration of less than ten years of diabetes (Figure 2). The mean duration of diabetes of patients was 8.54yrs with a standard deviation of 3.21.

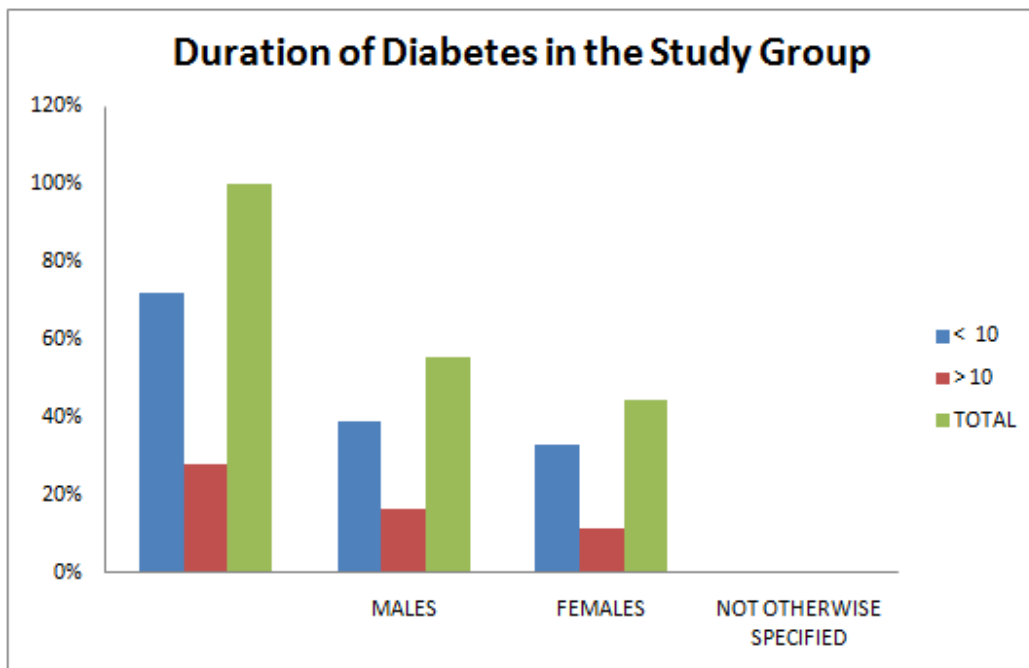


Figure 2: Duration of diabetes in the study group

All the patients in the study were also evaluated for Body Mass Index, and it was found that around 80 % were either overweight or obese. Details are clearly shown in Figure 3.

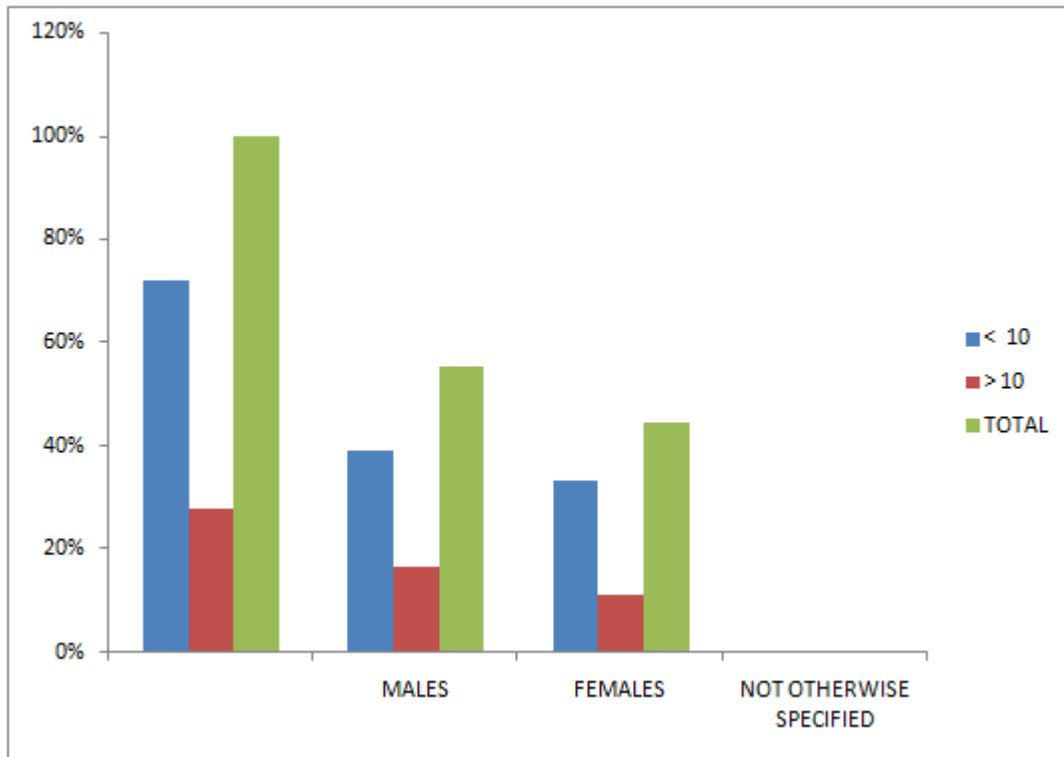


Figure 3: Distribution of body mass index values in the study population

Echocardiography was done in all patients. E/A ratio that is Peak velocity of early mitral flow/ Peak velocity of late mitral flow was less than 1 in 85 % of cases whereas it was between 1 to 2 in the remaining 15 % of cases (Figure 4). E/A ratio is the most specific and sensitive indicator of diastolic dysfunctions.

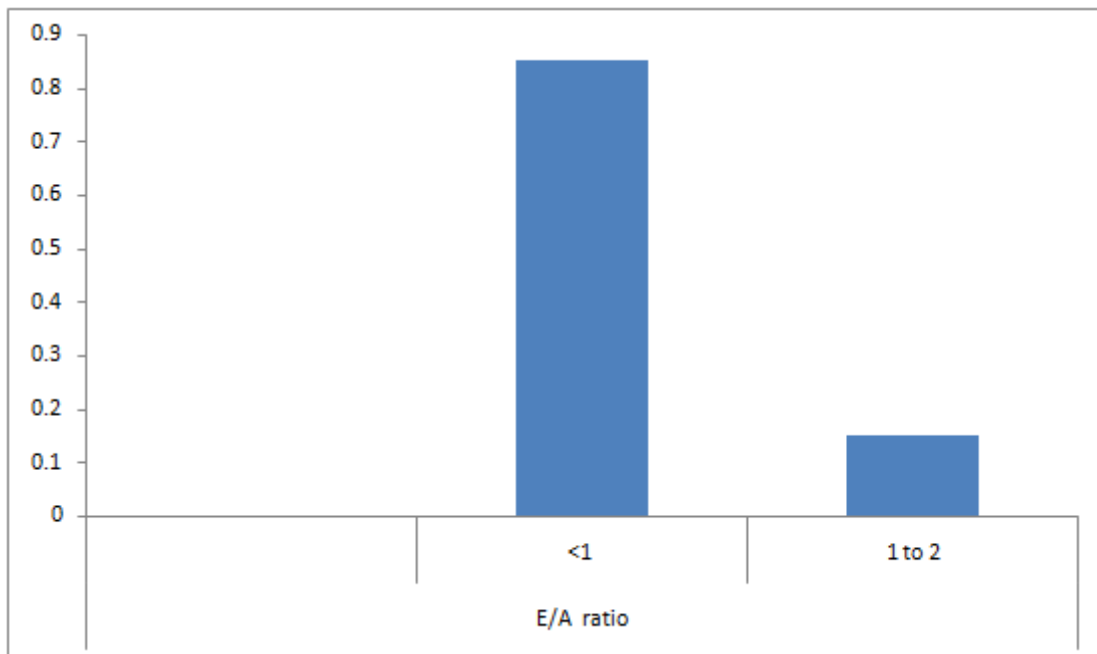


Figure 4: E/A ratio in the study group

IVRT that is Isovolumetric Relaxation Time was higher than 100 millisecond in 65% of cases where as it was between 60 and 100 in the remaining 35% of cases (Figure 5).

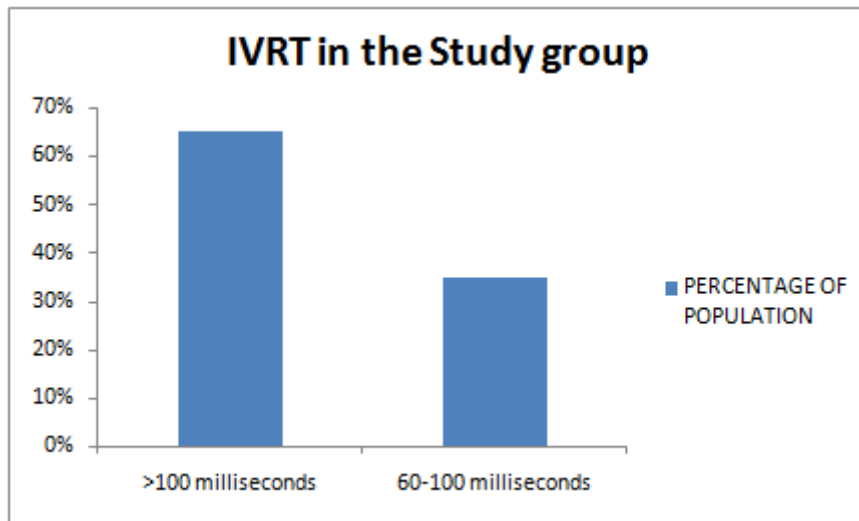


Figure 5: IVRT in the study group

Moreover, Deacceleration Time of E (Peak velocity of early mitral flow) was higher than 200 milliseconds in 69 % of cases whereas it was between 150 and 200 milliseconds in remaining 31 % (Figure 6).

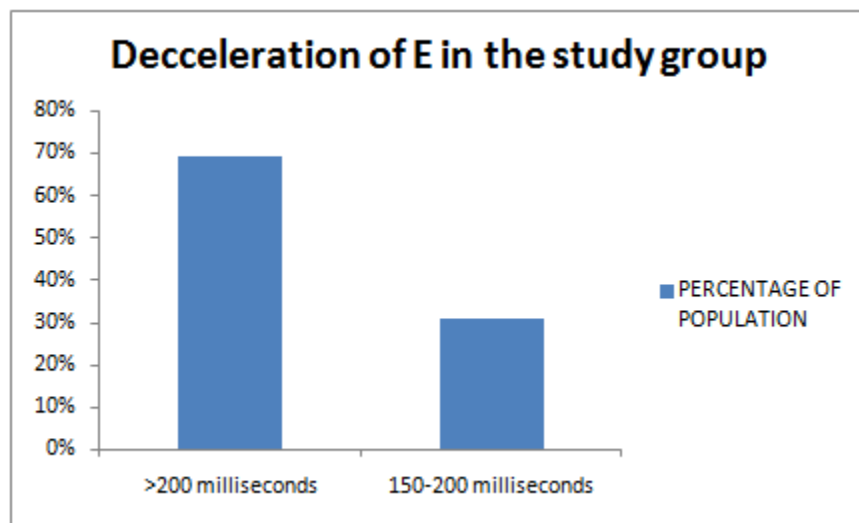


Figure 6: Deacceleration of E in the study group

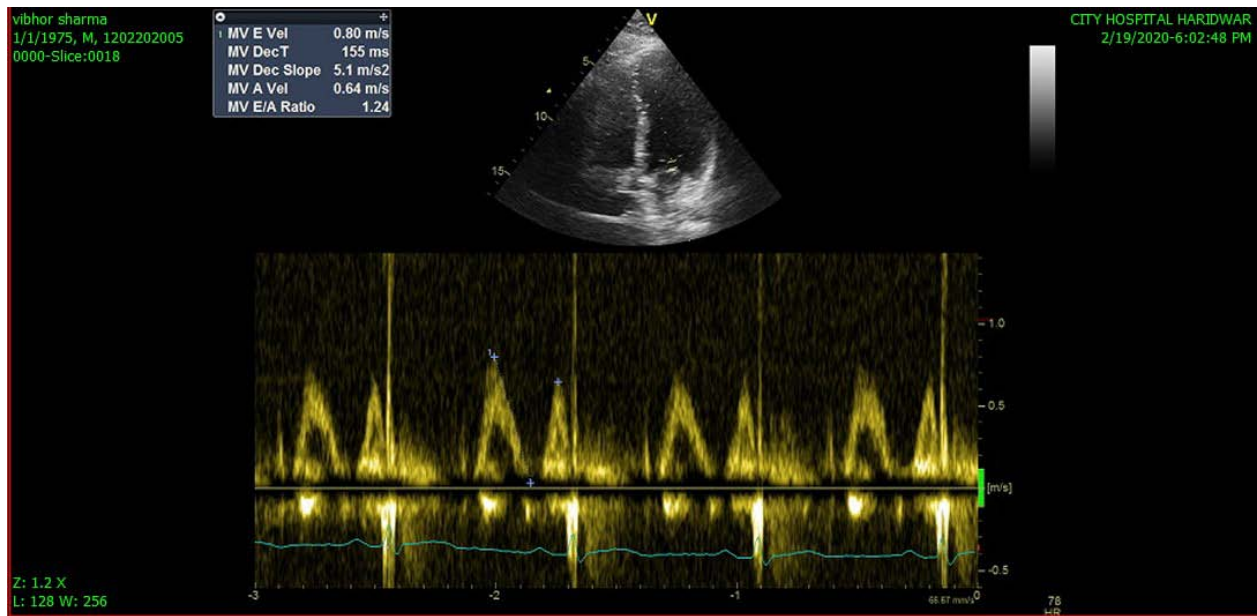


Figure 7: Normal mitral inflow pattern. E>A, E-early inflow wave: A-atrial contraction

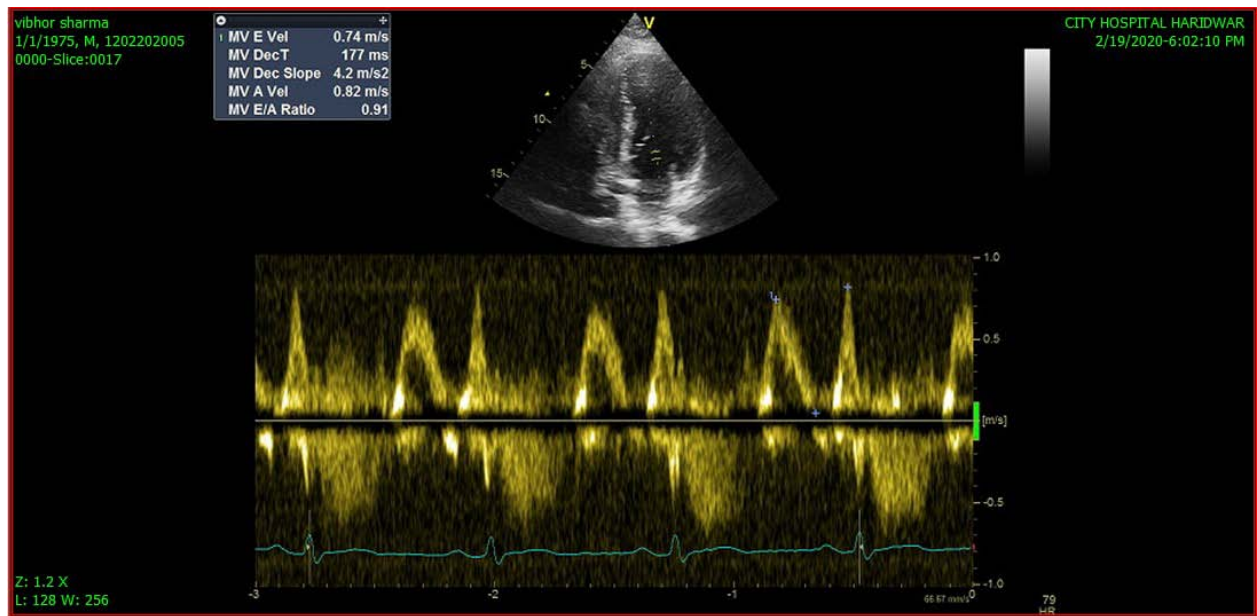


Figure 8: Delayed relaxation abnormality. Reversed E/A ratio (E/A<1)

IV. DISCUSSION

Diabetic cardiomyopathy has been proposed as an independent cardiovascular disease, and left ventricular diastolic dysfunction may represent the first stage of diabetic cardiomyopathy. It has been related to an increase in left ventricular wall thickness and myocardial mass and, early in the process, signs of myocardial diastolic dysfunction occur.⁶ There is experimental and clinical evidence of enhanced cellular apoptosis with myocyte loss as a consequence of oxidative stress induced by hyperglycaemia.⁷ Sanderson et al. suggested that impairment of the diastolic function of the left ventricle, i.e., its filling abnormalities are far more common than systolic dysfunction.⁸ The present

study reports left ventricular dysfunction by m-mode, 2-D echo, and color Doppler studies.

We can easily infer that the late atrial filling wave (A) was significantly increased, probably due to elevated LV filling pressure secondary to impaired relaxation among diabetic individuals. The diastolic abnormalities in diabetic patients most likely indicate reduced LV compliance secondary to small vessel disease, infiltrative myocardial process, metabolic derangement, or a combination of the three. Hence, our study clearly outlines the ongoing cardiac damage in diabetic patients even when the blood pressure stays within the normal range.

V. CONCLUSION

Though invasive procedures like Coronary Angiography and Scintigraphy are Gold Standard in demonstrating the Cardiovascular Compromise in suspected patients, Echocardiography serves as a gold standard screening tool in detecting early functional changes in heart, especially in diabetic patients. We strongly recommend it to be included in routine investigations leading to the work of diabetic patients.

Conflict of Interest: NIL

Funding: No funding required to carry out the present research work.

Ethical Clearance: Study was conducted in accordance with WMA (World Medical Association) Declaration of Helsinki, June 1964.

REFERENCES RÉFÉRENCES REFERENCIAS

1. Park K. Diabetes mellitus – Epidemiology of chronic non-communicable diseases and condition. Chapter 6. In: Parks Textbook of Preventive Social Medicine. 17th edition. India: Banarsidas Bhanot 2002; 294.
2. Munichoodappa C. Epidemiology and burden of type 2 diabetes mellitus. In: Type 2 diabetes – The Indian scenario, Jayaram BM (ed). Bangalore: Microlabs Ltd 2002; 13.
3. David SH Bell. Diabetes Care 2003 Oct; 26(10):2949-2951, 2791.
4. Ramachandran A. High prevalence of diabetes in urban population in South India. BMJ 1988; 297:587-590.
5. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care. 2001; 24:1614-9.
6. Ahmed SS, Jaferi GA, Narang RM, Regan TJ. Preclinical abnormality of left ventricular function in diabetes mellitus. Am Heart J. 1975;89:153-8.61.
7. Frustaci A, Kajstura J, Chimenti C, et al. Myocardial cell death in human diabetes. Circ Res. 2000;87: 1123-32.
8. Diabetic cardiomyopathy? An echocardiographic study of young diabetics. Br Med J 1978; 1:404.



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The Effect of Handgrip Exercises on Blood Pressure

By Faten A. Hamza & Reham E. Elden

Abstract- Background: Hypertension is a major risk factor that contributes to cardiovascular disease, including coronary artery disease, stroke, and heart failure.

Aim of the study: That handgrip exercises may also be effective for assisting with blood pressure management and adjust ability of a low-intensity working.

Methods: Twenty high normal and prehypertensive individuals without pharmacological, aged between 50 and 65 years, males and Females, conducted with handgrip exercises for 8 weeks. Participant's performed 4×2 minute isometric handgrip exercises with their non-dominant hand, each separated by a 3-minute rest period, 3 days a week.

Results: Blood pressure measurements were conducted at baseline and at the end of the protocol using a wrist blood pressure monitor. Eight weeks of isometric resistance training resulted in a 7-mmHg reduction of resting systolic blood pressure (SBP) (136 ± 12 to 129 ± 15); ($P=0.04$). Reductions of 4mmHg were also seen in mean arterial pressure (MAP) (100 ± 8 to 96 ± 11); ($P=0.04$).

Keywords: hypertension, handgrip exercises.

GJMR-I Classification: NLMC Code: WM 405



Strictly as per the compliance and regulations of:



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Conclusion: Handgrip exercise of maximum voluntary contraction significantly reduced SBP and MAP. Isometric handgrip (IHG) exercise training might be a simple, effective, inexpensive and non-pharmacological method in lowering blood pressure.

Keywords: hypertension, handgrip exercises.

I. INTRODUCTION

Evidences show that every year, worldwide 9.4 million people deaths die from complications of hypertension, which has become a global public health problem.(1) Hypertension is a major risk factor that contributes to cardiovascular disease, including coronary artery disease, stroke, and heart failure.(2,3) Additionally risk factors increased the prevalence of hypertension include population growth, increased age and behavioral risk factors, such as unhealthy diet, tobacco use, consumption of alcohol, excess weight, exposure to persistent stress, high cholesterol, diabetes mellitus, and lack of physical activity. Furthermore, Strategies implemented to prevent and manage hypertension include reducing exposure to behavioral risk factors and early detection and treatment of hypertension. (4) That found a Prehypertension is

characterized by systolic blood pressure of 120–139 mmHg and diastolic blood pressure of 80–89 mmHg, measured at rest.(5) High total peripheral resistance is the most commonly reported mechanism for the mildly increased blood pressure in hypertension, which is often accompanied by decreased arterial compliance.(6) Although it is unclear whether these changes occur in prehypertension.(21) Hypertension is responsible for 45% of cardiovascular deaths owing to heart disease and 51% owing to stroke worldwide.(1) Antihypertensive medications are effective at controlling blood pressure and have minimal side effects; however, only half the people with hypertension reach treatment goals.(38) Current first-line treatment for hypertension is non-pharmacological lifestyle modification including eating healthy diet, cessation of smoking, and increasing physical activity. (2,3,35) Currently, the recommended exercise program for blood pressure management in adults is dynamic endurance aerobic exercise of at least 150-minute moderate intensity, 75-minute vigorous intensity, or an equivalent combination of both each 1 week, as well as at least 2 days of muscle strengthening.(7) They found one important factor that may impact the effectiveness to lower blood pressure (BP) is the type of exercise performed. Analyses suggest isometric exercise may elicit BP reductions greater than those seen with dynamic aerobic and resistance exercise. (33, 34) However, isometric handgrip activity may become a new tool in the non-pharmacological treatment of high BP.(30,32) Isometric exercise involves sustained contraction against an immovable load or resistance with no or minimal change in length of the involved muscle group. Aerobic exercise performance has been shown to be inversely related to hemodynamic measurements.(38) Recent analyses suggest that isometric resistance training (IRT) may elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise.(2,8,9) A recent systematic review and subsequent meta-analysis confirms previous findings that IRT reduces systolic blood pressure (SBP) by almost 7mmHg, whereas diastolic blood pressure (DBP) and mean arterial pressure (MAP) were both lowered by almost 4mmHg. (2) Low-to moderate-intensity isometric handgrip exercise can be performed anywhere, requires relatively inexpensive equipment, and does not elicit the same level of cardiovascular stress as aerobic exercise.(2) Although most evidence indicates that greater handgrip

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strength is associated with lower BP. (23,24) Recent work suggests that IRT may become a new tool in the non-pharmacological treatment of high blood pressure. (10,12) males and individuals aged ≥ 45 years, may acquire greater blood pressure reductions from IRT (13). Randomized controlled studies of IRT, for ≥ 4 weeks in duration, have predominately used a 30% maximum voluntary contraction (MVC) and a sedentary control. (9) Ray and Carrasco (14) utilized a sham group, which held a handgrip dynamometer, but did not generate any force. Previous studies have utilized a low intensity during isometric leg training. (15, 16) We have found no reported studies, which have utilized an intensity $< 10\%$ MVC handgrip exercise with prehypertensive and/or hypertensive participants. In addition, previous studies of 4 to 10 weeks duration have focused on people aged between 20 and 35 years or 60 and 80 years with a sedentary control. In addition isometric handgrip study with 10 participants aged 52 ± 5 over 6 weeks have conduct. (17)

II. METHODS

This study conduct on Port Said Hospital extended from April 2018 to January 2019. The participants with high normal and pre hypertensive, aged between 50 and 65 years recruited from out Hospital clinic. Participants from males and Females had a resting SBP ≥ 130 mmHg and/or a resting DBP ≥ 85 mmHg, were receiving pharmacotherapy to treat their BP. written informed consent. Participants were excluded if they had known cardiovascular disease or multiple comorbidities, smokers, carpal tunnel, and arthritis which may have been aggravated with handgrip exercise. Participant baseline characteristics are displayed in. Participants trained 3 days per week for 8 weeks non-dominant hand. Participants then completed 4 sets of 2-minute isometric handgrip contractions separated by 3-minute rest periods.

Table 1: Entheroment

| Characteristics | |
|------------------------|--------------|
| Male | (n)7 |
| Female | (n)11 |
| Age, y | 58 ± 6 |
| Height, cm | 170 ± 9 |
| Weight, kg | 88 ± 16 |
| BMI, kg/m ² | 30 ± 6 |
| (SBP), mmHg | 136 ± 12 |
| (DBP) mmHg | 77 ± 7 |
| (MAP)mmHg | 100 ± 8 |
| (H R)bpm | 67 ± 9 |

Pre and post intervention blood pressure was established to assess resting SBP, DBP, heart rate (HR), and MAP. The wrist blood pressure monitor method to enable continuous noninvasive BP measurements. All post tests were conducted 24 hours after the final day of week 8 IRT and within 2 hours of the initial pretesting time of day. Blood pressure was measured in the participants' dominant arm Baseline and 24-hour post-IRT blood pressure measurements were conducted with the participant lying supine, with their arm relaxed by their side. Spss version was used to calculate the mean

and standard deviation for the last 15, 30, 60, and the entire 120seconds of baseline and post-IRT recording.

III. RESULTS

20 participants who completed the 2 months study of IRT, to establish the size of reduction in blood pressure, a 120-second resting baseline blood pressure recording was taken before and 24hours post-IRT Paired t test (Table 2).

Table 2

| | Mean, s | | P |
|-----------|--------------|--------------|-------|
| | Pre | post | |
| Systolic | 136 ± 12 | 129 ± 15 | 0.04* |
| Diastolic | 77 ± 7 | 75 ± 9 | 0.21 |
| MAP | 100 ± 8 | 96 ± 11 | 0.04* |
| HR | 67 ± 9 | 69 ± 11 | 0.37 |

Data are expressed as mean \pm SD. Pre: assessment before the start of the IRT program of Systolic blood pressure in comparison to Post, * P < 0.04, and MAP. * P < 0.04 in comparison to Post.

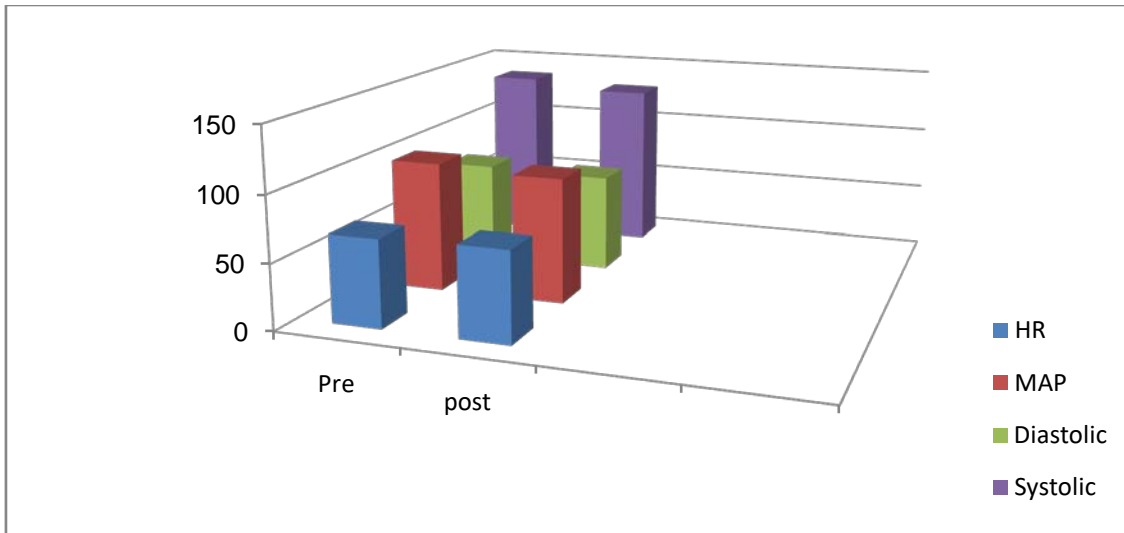


Figure 1

Table 3: Comparison of effect of Systolic sampling duration

| Systolic(mmHg) | 15 s | 30s | 60s | 120s | ANOVA (F) | P |
|----------------|--------|--------|--------|--------|-----------|------|
| Pre | 135±13 | 135±13 | 135±13 | 136±12 | 0.482 | 0.58 |
| Post | 129±16 | 128±16 | 129±16 | 129±15 | 0.414 | 0.67 |
| P | 0.07 | 0.06 | 0.06 | 0.04* | | |

Table 3 exhibits comparisons between 15, 30, and 60-second sampling, against the 120-second Systolic blood pressure recording

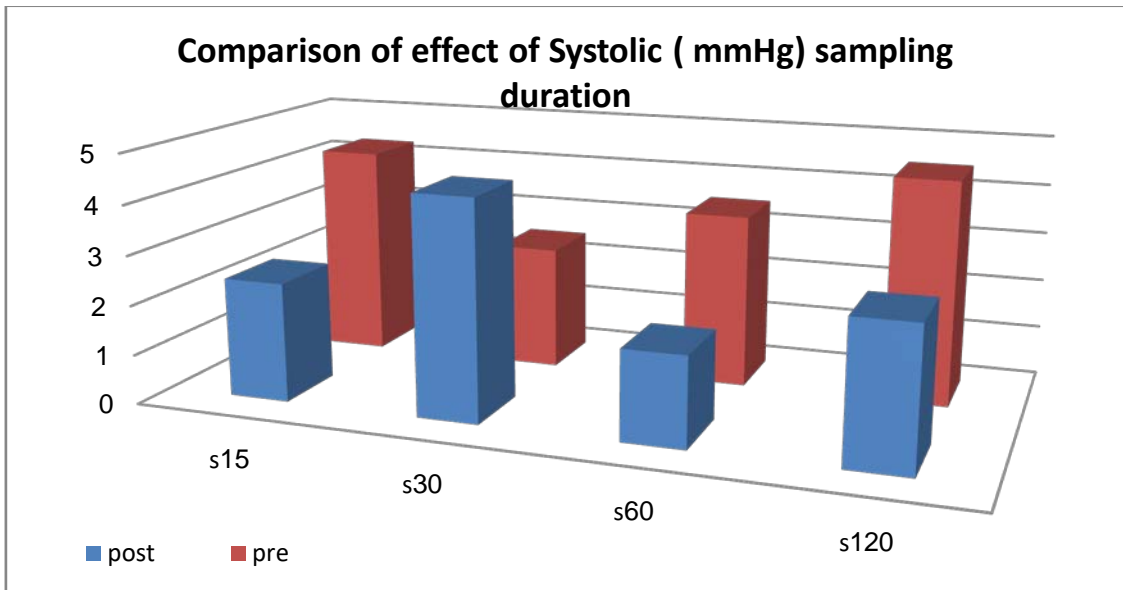


Figure 2

Table 4: Comparison of effect of Diastolic sampling duration

| Diastolic(mmHg) | 15 s | 30s | 60s | 120s | ANOVA (F) | P |
|-----------------|------|------|------|------|-----------|------|
| Pre | 76±7 | 76±7 | 77±7 | 77±7 | 2.204 | 0.13 |
| Post | 75±9 | 74±9 | 74±9 | 75±9 | 0.120 | 0.86 |
| p | 0.43 | 0.32 | 0.27 | 0.21 | | |

Table 4 exhibits comparisons between 15, 30, and 60-second sampling, against the 120-second Diastolic blood pressure recording

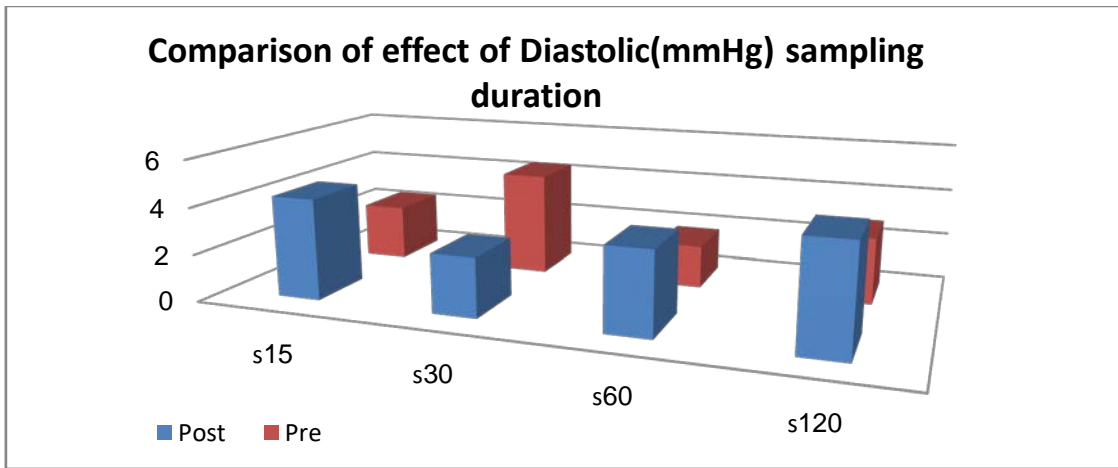


Figure 3

Table 5: Comparison of effect of MAP sampling duration

| MAP(mmHg) | 15 s | 30s | 60s | 120s | ANOVA (F) | P |
|-----------|-------|-------|-------|-------|-----------|------|
| Pre | 99±9 | 99±9 | 99±9 | 100±8 | 1.466 | 0.25 |
| Post | 95±11 | 95±11 | 95±11 | 96±11 | 0.143 | 0.87 |
| P | 0.12 | 0.07 | 0.05* | 0.04* | | |

Table 5 exhibits comparisons between 15, 30, and 60-second sampling, against the 120-secondMAP recording

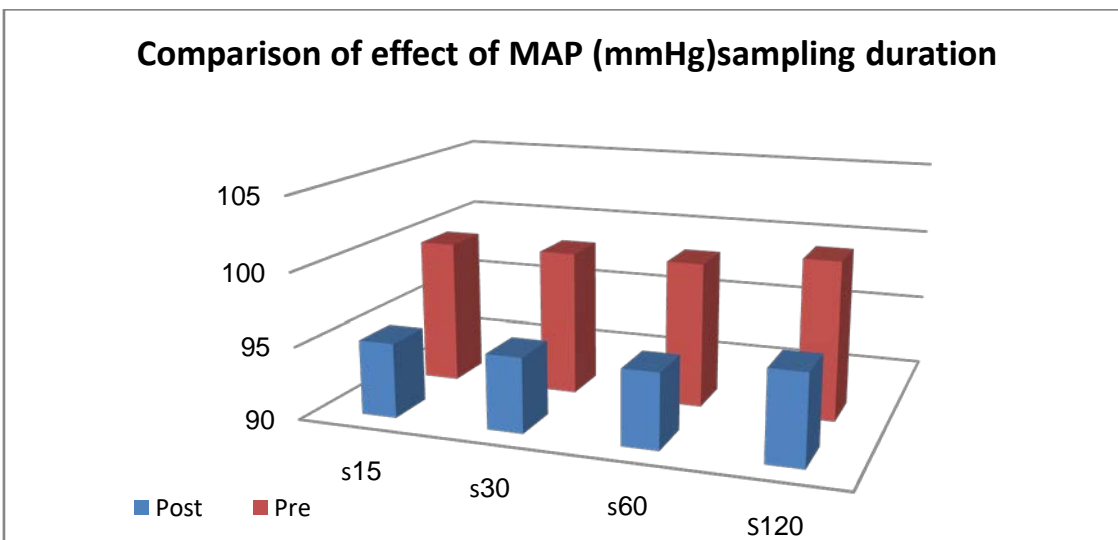


Figure 4

Table 6: Comparison of effect of HR sampling duration

| HR(bpm) | 15 s | 30s | 60s | 120s | ANOVA (F) | P |
|---------|-------|-------|-------|-------|-----------|------|
| Pre | 67±9 | 67±9 | 67±9 | 67±9 | 0.247 | 0.71 |
| Post | 69±12 | 69±11 | 69±11 | 69±11 | 0.814 | 0.42 |
| P | 0.33 | 0.34 | 0.43 | 0.37 | | |

Table 6 exhibits comparisons between 15, 30, and 60-second sampling, against the 120-secondHR recording



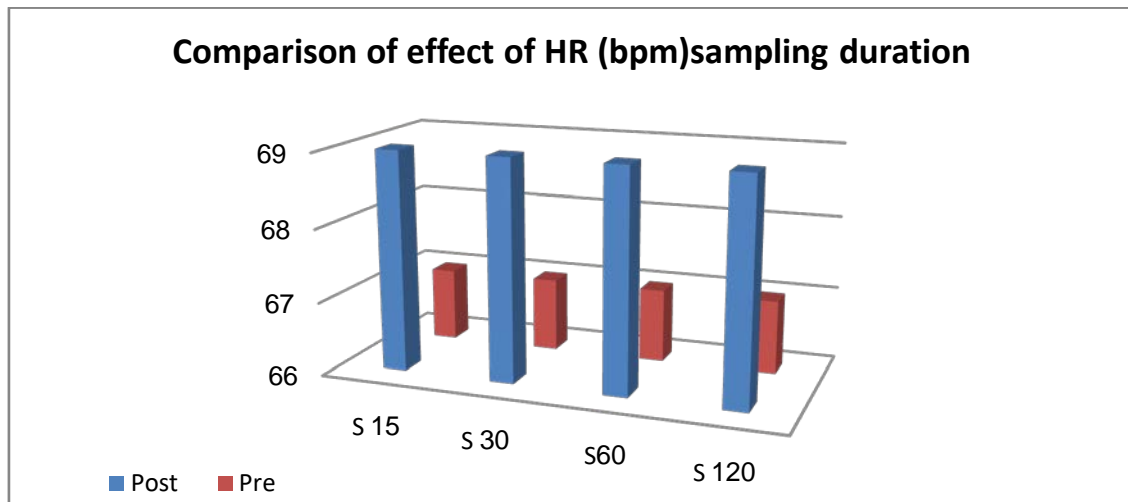


Figure 5

Wrist blood pressure monitor measurements were Paired t test analysis of blood pressure, MAP, and HR. Two months of isometric handgrip training resulted in a significant reductions were 7-mmHg reduction in baseline versus post intervention SBP of ($p=0.04^*$). Paired t test however, there were no significant reductions in DBP. Significant reductions were observed in MAP from baseline to post intervention of 4mmHg ($p=0.04^*$) in (Table 5). Analysis indicated an unchanged HR ($P=0.37$). ANOVA measures for 15, 30, 60, and 120seconds of pre- and post-resting SBP, DBP, MAP, and HR showed that the only data with statistically significant variation across the 4 measurements, the SBP and MAP as seen in Table 2 were significant with * $P < 0.04$, Based on this analysis, it was determined that the 120-second data were more stronger.

IV. DISCUSSION

The main finding of this study was that significant reductions in SBP and MAP in individuals conducting IRT for 8 weeks. The reduction in SBP was clinically significant 7mmHg and MAP 4 mmHg. The 5reduction in SBP is considered clinically meaningful ($>3\text{mmHg}$). (24, 25) Evidence demonstrated, the effect of isometric handgrip exercise on reducing BP in normotensive and hypertensive populations.(22) In addition, the positive associations between handgrip strength and BP explained the mechanism that Peripheral vascular resistance increases with chronological age due to reduced sympatholytic, which results in an elevated sympathetic tone. (19, 18) And vascular resistance increased with morphological changes in the arteriolar network. (11) Furthermore, BP is associated with the age-associated loss of lean mass. (37, 36) The results seen in this study reflect those seen in previous IRT studies, which also demonstrated significant reductions in SBP over an 8-week period.

(2,35,8,13) When baseline blood pressure was added as a covariate, secondary analysis showed that SBP, DBP, MAP, and HR were all significantly reduced. Although it is unclear whether the size of these reductions is clinically meaningful, it found that the magnitude of blood pressure reductions following IRT is directly related to pre-training blood pressure levels(26)Which could perhaps be explained by regression to the mean. Mean DBPs at baseline in our study were within the normal range, having population baseline mean $<85\text{mmHg}$. Taking into account the limited potential for further reductions in DBP, we did not expect to see much of a reduction in DBP after IRT intervention in either group. No significant reduction in DBP. Some small studies have failed to show DB Predictions; Howden et al(27) who had 8 participants conducting 5 weeks of IRT and Taylor et al.(28) with 9 participants after 10weeks of IRT, saw no statistical reductions in DBP with baseline $<85\text{mmHg}$. In contrast, both single studies (29) and pooled analyses from several studies (2,8,10) have shown significant reductions in DBP after IRT. Although baseline DBP may predict significant responses to IRT, again it is unclear whether the size of these reductions is clinically meaningful. The significant reduction in MAP lowered from 100 to 96mmHg, which is clinically meaningful. Reductions in MAP were also seen by Carlson et al (2) and Millar et al.(35)No changes in HR, The absence of change in resting HR indicates that IRT has a minimal effect on the parasympathetic nervous system. Other analyses have failed to show a reduction in HR with IRT when conducting an isometric handgrip protocol. (29, 31)The results of this study confirmed the overall that IRT lowers SBP, DBP and MAP. The magnitude of effect may be larger in hypertensive males aged ≥ 45 years, using unilateral arm IRT for 48 weeks. (39)

V. CONCLUSION

Reduction in SBP after 8 weeks of IRT, indicating that IRT may be an alternative exercise for people who are unable to reach the current recommendations of 2.5 hours of weekly aerobic exercise, to aid in their blood pressure management. IHG exercise training might be a simple, effective, inexpensive and non-pharmacological method in lowering blood pressure.

REFERENCES RÉFÉRENCES REFERENCIAS

- Lim S, Vos T, Flaxman A, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet*. 380:2224–2260, 2012.
- Carlson D, Dieberg G, Hess N, et al. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. *Mayo Clin Proc*. 89:327–34, 2014.
- Chobanian A, Wright J, Roccella E, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 42:1206–52, 2003.
- Brook R, Appel L, Rubenfire M, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. *Hypertension*. 61:1360–1383, 2013.
- Ramos RA, Guimaraes FS, Cordovil I, de Sa Ferreira A. The six-minute walk distance is a marker of hemodynamic-related functional capacity in hypertension: a case control study. *Hypertens Res* 2014; 37: 746–752.
- Ferrier KE, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM, et al. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *J Am Coll Cardiol*. 39:1020–5, 2002.
- Mozaffarian D, Fullerton HJ, Howard VJ, et al. Heart disease and stroke statistics—2016 update: a report From the American Heart Association. *Circulation* .133:e38–60, 2015.
- Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*.2:1–9, 2013.
- Millar PJ, McGowan CL, Cornelissen VA, et al. Evidence for the role of isometric exercise training in reducing blood pressure: potential mechanisms and future directions. *Sports Med*.44:345–56, 2014.
- Kelley GA, Kelley KS. Isometric handgrip exercise and resting blood pressure: a meta-analysis of randomized controlled trials. *J Hypertens*.28:411–8, 2010.
- Bearden SE. Effect v of aging on the structure and function of skeletal muscle microvascular networks. *Microcirculation*. 13:279–288, 2006
- Badrov MB, Horton S, Millar PJ, et al. Cardiovascular stress reactivity tasks successfully predict the hypotensive response of isometric handgrip training in hypertensives. *Psychophysiology*. 50:407–14, 2013.
- Inder JD, Carlson DJ, Dieberg G, et al. Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. *Hypertens Res* .39:88–94, 2015.
- Ray CA, Carrasco DI. Isometric handgrip training reduces arterial pressure at rest without changes in sympathetic nerve activity. *Am JPhysiol Heart CircPhysiol*.279:245–9, 2000.
- Baross AW, Wiles JD, Swaine IL. Effects of the intensity of leg isometric training on the vasculature of trained and untrained limbs and resting blood pressure in middle-aged men. *Int J Vasc Med* .2012:964–7, 2012.
- Wiles JD, Coleman DA, Swaine IL. The effects of performing isometric training at two exercise intensities in healthy young males. *Eur J ApplPhysiol*.108:419–28, 2010.
- Peters PG, Alessio HM, Hagerman AE, et al. Short-term isometric exercise reduces systolic blood pressure in hypertensive adults: Possible role of reactive oxygen species. *Int J Cardiol*.110:199–205, 2006.
- Parker BA, Smithmyer SL, Jarvis SS, Ridout SJ, Pawelczyk JA, Proctor DN. Evidence for reduced sympatholysis in leg resistance vasculature of healthy older women. *Am J Physiol Heart Circ Physiol*. 292: 1148–1156, 2007.
- Hansen J, Sander M, Thomas GD. Metabolic modulation of sympathetic vasoconstriction in exercising skeletal muscle. *Acta Physiol Scand*. 168:489–503, 2000.
- Truijen J, van Lieshout JJ, Wesselink WA, et al. Noninvasive continuous hemodynamic monitoring. *J ClinMonitComput*.26:267–78, 2012.
- Kingwell BA. Large artery stiffness: Implications for exercise capacity and cardiovascular risk. *Clin Exp Pharmacol Physiol*. 29:214–7, 2002.
- Millar PJ, McGowan CL, Cornelissen VA, Araujo CG, Swaine IL. Evidence for the role of isometric exercise training in reducing blood pressure: potential mechanisms and future directions. *Sports Med*. 44:345–356, 2014.
- Hess NC, Carlson DJ, Inder JD, Jesulola E, McFarlane JR, Smart NA. Clinically meaningful blood pressure reductions with low intensity isometric handgrip exercise. A randomized trial. *Physiol Res*. 65:461–468, 2016.
- Kelley GA, Kelley KS. Isometric handgrip exercise and resting blood pressure: a meta-analysis of

- randomized controlled trials. *J Hypertens.* 28:411–418, 2010.
25. Wong GW, Wright JM. Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. *Cochrane Database Syst Rev*2014; CD007452.
 26. Millar PJ, Bray SR, McGowan CL, et al. Effects of isometric handgrip training among people medicated for hypertension: a multilevel analysis. *Blood Press Monit.*12:307–14, 2007.
 27. Howden R, Lightfoot JT, Brown SJ, et al. The effects of isometric exercise training on resting blood pressure and orthostatic tolerance in humans. *Experiment Physiol.*87:507–15, 2002.
 28. Taylor AC, McCartney N, Kamath MV, et al. Isometric training lowers resting blood pressure and modulates autonomic control. *Med Sci SportsExerc.*35:251–6, 2003.
 29. Millar PJ, Bray SR, MacDonald MJ, et al. The hypotensive effects of isometric handgrip training using an inexpensive spring handgrip training device. *J CardiopulmRehabilPrev.*28:203–7, 2008.
 30. Owen A, Wiles J, Swaine I. Effect of isometric exercise on resting blood pressure: a meta-analysis. *J Hum Hypertens* 24: 796–800, 2010.
 31. Millar PJ, Bray SR, MacDonald MJ, et al. Cardiovascular reactivity to psychophysiological stressors: association with hypotensive effects of isometric handgrip training. *Blood Press Monit.*14:190–5, 2009.
 32. Kelley GA, Kelley KS. Isometric handgrip exercise and resting blood pressure: A meta analysis of randomized controlled trials. *J Hypertens.*28: 411–418, 2010.
 33. Carlson DJ, Dieberg G, Hess N, Millar P, Smart NA. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. *Mayo ClinProc*2014; 89.
 34. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2013; 2: e004473.
 35. Millar PJ, Levy AS, McGowan CL, et al. Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients. *Scand J Med Sci Sports.* 23:620–6, 2013.
 36. Corish CA, Kennedy NP. Anthropometric measurements from a cross-sectional survey of Irish free-living elderly subjects with smoothed centile curves. *Br J Nutr.* 89:137–145,2003.
 37. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol.* 88:1321–1326, 2000.
 38. Nuckols TK, Aledort JE, Adams J, et al. Cost implications of improving blood pressure management among U.S. adults. *Health Serv Res.*46:1124–57, 2011.
 39. Jodie D I, Deborah J C, Gudrun D, James R M, Nicole CL and Neil A. Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. *Hypertension Research.* 39: 88–94, 2016.



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A Randomized Trial. Comparing Herniorrafia Modifield Desarda Repair and Hernioplastia Lichtenstaein Repair for Inguinal Hernia. (Study of 1243)

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Abstract- Introduction: The objective of this study is to compare the outcomes of Modified Desarda repair no mesh and Lichtenstein repair for inguinal hernia.

Patients and Methods: This is a prospective randomized controlled trial study of 1242 patients having 1313 hernias operated from January 2008 to December 2018. 640 patients were operated using Lichtenstein repair and 602 using Desarda repair. The variables like age, sex, location, type of hernia, tolerance to local anesthesia, duration of surgery, pain on the first, third and fifth day, hospital stay, complications, re-explorations, morbidity and time to return to normal activities were analyzed. Follow up period was from 1-10 years (median 6.5 years).

Results: There were no significant differences regarding age, sex, location, type of hernia, and pain in both the groups. The operation time was 52 minutes in Modified Desarda group and 42 minutes in the Lichtenstein group that is significant ($p < 0.05$).

Keywords: *desarda repair; inguinal hernia; lichtenstein repair; randomized trial.*

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A Randomized Trial. Comparing Herniorrafia Modifield Desarda Repair and Hernioplastia Lichtenstaein Repair for Inguinal Hernia. (Study of 1243)

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Results: There were no significant differences regarding age, sex, location, type of hernia, and pain in both the groups. The operation time was 52 minutes in Modified Desarda group and 42 minutes in the Lichtenstein group that is significant ($p < 0.05$). The recurrence was 0.0 % in Modified Desarda group and 0.3 % in Lichtenstein group. But, there were 8 cases of infection to the polypropylene mesh in the Lichtenstein group, 2 of this required re-exploration. The morbidity was also significantly more in Lichtenstein group (7.0 %) as compared to Modified Desarda group (3.6 %). The mean time to return to work in the Modified Desarda group was 8.26 days while a mean of 12.58 days was in the Lichtenstein group. The mean hospital stay was 29 hrs. in Modified Desarda group while it was 49 hours in the Lichtenstein group in those patients who were hospitalized.

Conclusions: Modified Desarda repair scores significantly over the Lichtenstein repair in all respects including re-explorations and morbidity. Modified Desarda repair is a better choice as compared with Lichtenstein repair.

Keywords: *desarda repair; inguinal hernia; lichtenstein repair; randomized trial.*

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I. INTRODUCTION

In 1890, Eduardo Bassini described suture repair for inguinal hernia. This was a massive leap forward and has been the basis of open repair for over 100 years. The surgeon enters the inguinal canal by opening its anterior wall, the external oblique aponeurosis. The spermatic cord is dissected free and the presence of a lateral or a medial hernia is confirmed. The sac of a lateral hernia is separated from the cord, opened and any contents reduced. The sac is then sutured closed at its neck and excess sac removed. If there is a medial hernia, then it is inverted and the transversalis fascia is suture plicated. Sutures, are now placed between the conjoint tendon above and the inguinal ligament below, extending from the pubic tubercle to the deep inguinal ring. The posterior wall of the inguinal canal is thus strengthened.¹ Over 150 modifications to the Bassini operation have been described with little or no benefit except for the Should ice modification. In this operation, the transversalis fascia is opened by a central incision from deep inguinal ring to the pubic tubercle and then closed to create a double-thick, two-layered posterior wall (double breasting). The external oblique is closed in similar fashion. Expert centres have reported lifetime failure rates of less than 2 per cent after Should ice repair but it is a technically demanding operation which, in general hands, gives results identical to the Bassini repair.^{1, 24.}

The surgeons use different techniques in Cuba for inguinal hernia repair like Bassini or Should ice and its modifications or different types of mesh repairs. The standard mesh is not available at many places and it is expensive also. Hernia treatment has become a health problem because of its social, economic and labour implications due to its high incidence in our population [1]. Until recently, the only parameters to be evaluated were recurrence, complication rates etc. Today, other parameters like cost, post-surgery wellbeing and quality of life have gained importance. The demand of general surgeons is to identify operations that are simple to perform without the need for complicated dissection and

with low complication and recurrence rates. Avoidance of use of foreign material where possible is a basic surgical principal. The authors read about the Desarda repair which seems be simple in concept, avoids the use of mesh and gives the desired results. This repair is based on the concept of providing a strong and physiologically dynamic posterior wall to the inguinal canal. An undetached strip of the aponeurosis of the external oblique muscle replaces the absent aponeurotic element in the posterior wall and the weakened conjoint muscle receives additional strength from the external oblique muscle to keep it physiologically dynamic [2]. There are still many controversies to answer. Which is the best technique for repair? [3] Is hernioplasty better than herniorrhaphy? Which is the best technique for hernioplasty or herniorrhaphy? Does laparoscopic surgery have a better cost-efficiency than open surgery? Is mesh necessary in all inguinal hernia repairs? The objective of this study is to re-evaluate the Lichtenstein mesh repair and compare it with the novel and “No mesh, physiological repair” described by Modified Desarda Technique.

II. METHOD

This study was designed as a RCT(Randomized Controlled Clinical Trial) among the 1313 patients (602 patients of Modified Desarda’s technique {modification of Desarda’s technique by adding Modified Bassini’s technique [Darn with continuoussuturing with non-absorbable polypropylenesuture]} and 640 patients of Lichtenstein procedure alone) of inguinal hernia in Surgery Unit 1 & 2, Enrique Cabrera Hospital, Havana Cuba from a period of January 2008 to December 2018 with a view to depict the short & intermediate term (05years) outcomes of newly proposed Modified Desarda’s technique in contrast to Lichtenstein procedure. All the patients from both sexes older than 16 years with primary and recurrent inguinal hernias were included. Patients operated on emergency basis were excluded. The diagnosis of inguinal hernia and its type was made by clinical examination. Information was given to the patients as regards the anesthetic procedures. The patient chose type of anaesthesia after discussion with the surgeon. The Randomization was

performed using a consecutively numbered, sealed envelope, which was opened, in theatre and all patients having an even number were operated by the Lichtenstein and uneven numbers by the modified Desarda technique. The operating surgeon completed a data sheet. The operating surgeon was at consultant level for all operations.

The evaluator was also a surgeon of consultant level. All patients signed a written informed consent. Approval of the local ethical committee was given prior to the onset of the study. Modified Desarda repair was performed according to the surgical technique described by Dr. Desarda and mesh prosthesis repair was undertaken as described in the textbooks. Prophylactic antibiotic was administered in the operating room before surgery (Cefazoline 1g.) in the Lichtenstein group only. All patients were discharged as soon as their post-surgical recovery allowed, and all patients were instructed to do daily, routine, non-strenuous work after discharge. A non-steroidal anti-inflammatory (Diclofenac) analgesic was prescribed for a period of 5 days and continued if required. The consultants followed all the patients at 8 days, 1 month, 6 months and then yearly thereafter. The consultants followed all the patients at 8 days, 1 month, 6 months and then yearly thereafter. A data sheet was completed by the operating surgeon including type of hernia (Nyhus classification) [4], anaesthesia, technical details and intra-operative complications. At discharge, further data was added including any early post-operative complications. Patients were asked to complete a pain score on the first, third and fifth day after surgery using a linear analogue scale [5,6]. At first follow up, one month after surgery, further data were collected including time to return to normal activities. The Student T test was used to compare the independent measures and the Mann Whitney-U test for non-parametric data. The Chi-squared test and Fisher’s exact test were used to measure the association between quality variables.

III. RESULTS

There was no significant difference in relation to sex, age, location and type of inguinal hernia in both the groups. (Table 1).

Table 1: Age, Sex, Location and Tipo of Hernia

| AGE,SEX,LOCALION | SURGICAL TECHNIQUE | | | |
|------------------|--------------------------|------|------------------------|------|
| | LICHTENSTEIN GROUP n=640 | | MODIFIELD DESRDA n=602 | |
| MEDIAN AGE | 57,3 | | 58,1 | |
| | No. | % | No. | % |
| SEX | | | | |
| MALE | 585 | 91,4 | 558 | 92,7 |
| FEMALE | 55 | 8,6 | 44 | 7,3 |
| LOCATION | | | | |
| RIGHT | 305 | 47,6 | 295 | 49,0 |
| LEFT | 291 | 45,4 | 280 | 46,5 |
| BILATERAL | 44 | | 27 | 4,5 |

| TYPE OF HERNIA | | | | |
|----------------|-----|------|-----|------|
| I Y II | 277 | 43,2 | 296 | 49,2 |
| IIIa IIIb | 313 | 49,0 | 279 | 46,3 |
| IV | 50 | 7,8 | 27 | 4,5 |

Local anesthesia was used in 279 patients in Lichtenstein group and 379 patients in the Desarda group. All those 658(53.0%) patients were operated on as outpatient basis without hospitalization. In the

remainder of 584 patients who were treated as in-patients, the mean hospital stay was 27 hours in Desarda group and 47 hours in the Lichtenstein group ($p < 0.05$) (Table 2).

Table 2: Anesthesia and Hospital Stay

| ANESTHESIA AND HOSPITALSTAY | SURGICAL | | TECHNIQUE | |
|-----------------------------------------|--------------------------|------|-------------------------|------|
| | LICHTENSTEIN GROUP n=640 | | MODIFIELD DESARDA n=602 | |
| | No. | % | No. | % |
| ANESTHESIA | | | | |
| LOCAL | 279 | 43,6 | 379 | 63,0 |
| SPINAL | 315 | 49,2 | 203 | 33,7 |
| GENERAL | 46 | 7,2 | 20 | 3,0 |
| HOSPITALIZATION | | | | |
| Outdoor surgery without Hospitalization | 273 | 42,6 | 377 | 62,6 |
| Short Term Hospitalization (<3days) | 310 | 48,4 | 211 | 35,0 |
| Long Term Hospitalization(>3days) | 57 | 9,0 | 14 | 2,4 |

Tolerance to local anesthesia was good during surgery in 68% and 67% respectively (NS). The mean duration of surgery was 42 minutes for Lichtenstein and

52 minutes for Desarda group ($p < 0.05$). Analysis of pain scores from day one to day 5 showed no significant difference (Table 3).

Table 3: Duration of Surgery and Pain

| DURATION TOLERANCE AND PAIN | SURGICAL | | TECHNIQUE | |
|-----------------------------|----------------------------|------|---------------------------------|------|
| | LICHTENSTEIN GROUP N = 640 | | MODIFIELD DESARDA GROUP N = 602 | |
| DURATION OF SURGERY | | | | |
| AVERAGE | 42 mts. | | 52 mts. | |
| | No. | % | No. | % |
| PAIN : MILD TO MODERATE | | | | |
| First Day | 333 | 52,0 | 348 | 57,8 |
| UP To Third Day | 230 | 36,0 | 194 | 32,2 |
| Upto Fifth Day | 77 | 12,0 | 60 | 10,0 |

There was no incidence of severe pain or chronic groin pain in both the groups

There was no incidence of severe pain in either group. The recurrence rate was 0.0 % in the Desarda group, and 0.3 % in the Lichtenstein group (NS). Four patients in the Lichtenstein group required re-exploration and mesh removal for the chronic suppuration. These patients had chronic suppuration, motivated by the rejection of the mesh which caused the mesh to be removed. Thus 0.5% of patients in the Lichtenstein group required a further surgical intervention for either recurrence or sepsis which was significantly higher than

the Desarda group ($p < 0.05$). All the patients were operated by the same surgeon and his helpers. (Table 4).

Table 4: Recurrence and Re-Exploration

| | | | | |
|------------------------------|---------------------------|------|--------------|--------|
| LICHTENSTEIN GROUP n=640 | 4 Mesh Removal for sepsis | 0,50 | 2 Recurrence | 0,30 % |
| MODIFIED DESARDA GROUP n=602 | - | - | 0 Recurrence | 0,00 % |

The seroma was the complication that most frequently occurred with 18 patients in both groups (1.4%). 45 (7.0%) patients developed post-operative complications in the Lichtenstein group and 22 (3.6%) patients showed complications in the Desarda group ($p < 0.05$) (Table 5).

Table 5: Morbidity

| MORBIDITY | SURGICAL TECHNIQUE | | | | | |
|-------------------------------|--------------------------|-----|--------------------------------|-----|--------------|-----|
| | Lichtenstein Group n=640 | | Modifield Desarda Group n= 602 | | Total n=1242 | |
| | No. | % | No. | % | No. | % |
| Seroma | 12 | 1,8 | 6 | 1,0 | 18 | 1,4 |
| Mild Infection | 8 | 1,2 | 6 | 1,0 | 14 | 1,1 |
| Hematoma | 7 | 1,0 | 4 | 0,6 | 11 | 0,8 |
| Orchitis | 5 | 0,7 | 2 | 0,3 | 7 | 0,5 |
| Testicular atrophy | 2 | 0,3 | - | - | 2 | 0,1 |
| Sepsis without re-exploration | 4 | 0,6 | - | - | 4 | 0,3 |
| Sepsis with re-exploration | 2 | 0,3 | - | - | 2 | 0,1 |
| Bradycardia | 4 | 0,6 | 4 | 0,6 | 8 | 0,6 |
| Recurrence | 2 | 0,3 | 0 | 0 | 2 | 0,1 |
| Total | 45 | 7,0 | 22 | 3,6 | 67 | 5,3 |

70,0 % patients returned to work within 8-15 days in the Desarda group with a mean of 13,4 days while 54,2 % patients returned to work within 8-15 days with a mean of 14.5 days in the Lichtenstein group, that is significant because in the Lichtenstein group the morbidity is higher than in the Desarda group. ($p < 0.05$) (Table 6).

| PATIENTS RETURNED TO WORK | SURGICAL TECHNIQUE | | | |
|---------------------------|---------------------------|------|------------------------------|------|
| | LICHTENSTEIN GROUP n= 640 | | MODIFIED DESARDA GROUP n=602 | |
| | No. | % | No. | % |
| 1-7 Days | 25 | 4,0 | 42 | 7,0 |
| 8-15 Days | 347 | 54,2 | 421 | 70,0 |
| 16-30 days | 268 | 41,8 | 139 | 23,0 |

Lichtenstein Group: Mean: 1-7 days: 6,8 days, 8-15 days: 14,5 days, 16-30 days: 21,3 days. Desarda Group Mean: 1-7 days: 5,7 days, 8-15 days: 13,4 days, 16-30 days: 18,4 days.

Table 6: Return to Work

There was no case of chronic groin pain lasting for more than 6 months in either of the groups. Follow up was complete in over 97% at 1 year, 92% at 2 years, 89% at 3 years, 83% at 4 years, 80% at 5 years, 80% at 6 years, 76% at 7 years, 73% at 8 years, 72% at 9 years and 70% at 10 years with no significant difference between the two operation groups.

IV. DISCUSSION

Mesh repair is now widely used in the developed world and is often referred to as the gold standard despite a relative paucity of clinical trials comparing mesh with suture repair. The cost of surgery [7] and the post-operative morbidity affecting the quality

of life are important considerations in the inguinal hernia surgery. There are no clear scientific evidences to prove that the mesh prosthetic repair is superior to the non-prosthetic repair in this respect [8]. There are advantages and disadvantages associated with all types of open inguinal hernia repairs. Existing non-prosthetic repair (Bassini/Shouldice) is blamed causing tissue

tension and mesh prosthetic repair is blamed for known complications of a foreign body. Dr. Desarda sutures an undetached strip of the external oblique aponeurosis between the muscle arch and the inguinal ligament to give a strong and physiologically dynamic posterior wall [9]. This results in a tension free repair without the use of any foreign body. Being simple to perform it eliminates disadvantage of technical difficulty seen with Shouldice repair.

Different studies have tried to give an answer as to which of the existing operation is best for inguinal hernia repair [10,11]. The EU Hernia Trialist collaboration [12] made a systematic revision of the randomized prospective studies and the analysis of the results of these different studies. It showed that the duration of surgery was less in hernioplasty in six studies, longer in three and equal in the remaining six. In our group, there was a significant but slight increase in operating time with the Desarda operation. Post-operative pain after mesh prosthetic repair may be less than after Shouldice repair because of reduced tension [12,13]. Our results have shown that there are no significant differences between the two groups for pain on the first to fifth day after surgery. We found no significant difference in analgesic requirements between the techniques. Overall morbidity was 4.5%, which is similar to the rates described in other studies (7-12%) [14]. The morbidity rate was higher after the Lichtenstein repair (34 cases, 6.0% versus 16, 3.0 % in the Modified Desarda group). There were 5 mesh infections after surgery in the Lichtenstein group. Two cases required partial excision of the mesh and in one case, it was associated with recurrence. Modified Desarda technique has lower morbidity as compared to mesh hernioplasty. We believe that the four cases of recurrences seen in Modified Desarda group were due to failure of proper lateralization of the cord and insufficient narrowing of the internal ring as advised by Desarda.

This was evident at re-exploration in those cases that needed only narrowing of the internal ring with few more stitches. In patients admitted to hospital, post-operative stays and the period required to return to normal work after surgery was also significantly in favour of the Modified Desarda group. 45 patients from Lichtenstein group required more than 3 days in the hospital due to local wound complications or for some other reasons compared to only 5 patients from the Modified Desarda group, a significant difference. We noted a marked difference in the type of anaesthetic used, 39% v 72% for local, 54% v 25% for spinal and 7% v 2% for general anaesthetic in Lichtenstein Modified Desarda group. This could affect the statistics of hospital stay of the patients who required hospitalization. The external oblique muscle technique satisfies all criteria of modern hernia surgery. It is simple and easy to do. It does not require risky or complicated dissection. There is minimal tension in the suture line. It

does not require any foreign material and it does not use weak muscle or fascia transversalis for repair. It does not use mesh prosthesis so it is more economical. No foreign body is required in the Desarda repair thus avoiding morbidity associated with foreign bodies including rejection, infection and chronic groin pain.

Jacek Szopinski, et al. [15] stated in their Randomized Controlled Trial (RCT) that the "Desarda technique" has the potential to enlarge the number of tissue based methods available to treat groin hernias. The most evident indications for use of the Modified Desarda technique include use in young patients, in contaminated surgical fields, in the presence of financial constraints, or if a patient disagrees with the use of mesh." Situma, et al. [16] compared Desarda technique with the modified Bassini technique in their RCT and concluded that there is no difference in short-term outcome between Desarda and modified Bassini inguinal hernia repair as regards resumption of normal gait and patterns of pain. Manyilira [17] concluded in their RCT that the efficacy of the Desarda technique in respect of the early clinical outcomes of hernia repair is similar to that of Lichtenstein method. However the operator in this study showed that the Desarda repair takes a significantly shorter operative time [18,19]. The authors therefore conclude that the Modified Desarda repair for inguinal hernia gives the same or better results when compared with the Lichtenstein Mesh repair with shorter hospital stay, more rapid recovery and avoidance of specific mesh related complications whilst also reducing the cost of surgery. It is technically simpler than the Shouldice repair and we recommend that surgeons become acquainted with this technique [20-23].

In a net Shell, the newly proposed Modified Desarda's technique (Combined approach of Desarda's & Modified Bassini's technique) is a more resilient repair for indirect inguinal hernia in terms of late recurrence in contrast to Desarda's procedure alone [24-26].

REFERENCES RÉFÉRENCES REFERENCIAS

1. Rutkow MI (1998) Epidemiologic, economic and sociologic aspects of hernia surgery in the United States in the 1900s. *Surg. North Am* 78: 941-951.
2. Desarda MP (2001) Inguinal herniorrhaphy with an undetached strip of external oblique aponeurosis: a new approach used in 400 patients. *Eur J. Surg* 167: 01-06.
3. Porrero JL, Bonachía O, López-Buenadicha A, Sanjuanbenito A, Sánchez-Cabezudo C (2005) Reparación de la hernia inguinal primaria: Lichtenstein frente a Shouldice. Estudio prospectivo y aleatorizado sobre el dolor y los costos hospitalarios. *Cir Esp* 77: 5-8.

4. Aragon FJ (2001) Nuevas técnicas protésicas para el tratamiento de 4. la hernia inguinal. Ediciones Avila 2001: 22-23.
5. Price DD, Bush FM, Long S, Harkins SW (1994) A comparison of pain 5. measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* 56: 217-226.
6. Porrero JL, Sanchez-Cabezudo C, Lee P (1998) Study of unilateral 6. post-herniorrhaphy analgesia with local anaesthetic and monitored anaesthesia care. *Ambulatory Surg* 6: 211-214.
7. Costos hospitalarios (2005) Comunicación personal. Departamento económico. Hospital Enrique Cabrera. Enero 2015.
8. Porrero JL (1999) El cambio de la cirugía de la hernia en la última 8. década. En: Celdran A., de la Pinta JC, editores. *Fundamentos de la hernioplastia sin tensión*. Madrid: Fundación Jiménez Díaz 1999: 9-11.
9. MP Desarda (2003) Surgical physiology of inguinal hernia repair-a 9. study of 200 cases. *BMC Surgery* 3: 1-9.
10. Simons MP, Kifignen J, Van Geldere D, Hoitsma HFW, Obertop H 10. (1996) Role of the Shouldice technique in inguinal hernia repair: a systematic review of controlled trials and meta-analysis. *Br J Surg* 83:734-738.
11. McGillicuddy JE (1998) Prospective randomized comparison of the 11. Shouldice and Lichtenstein hernia repair procedures. *Arch Surg* 133: 974-978.
12. EU Hernia Trialist Collaboration (2000) Mesh compared with non-mesh 12. methods of open groin hernia repair: systematic review of randomized controlled trials. *Br J Surg* 87: 854-859.
13. Kingsnorth AN, Porter Chs, Bennett DH, Walker AJ, Hyland ME, et al. 13. (2000) Lichtenstein patch or prefix plug and patch in inguinal hernia: a prospective double-blind randomized controlled trial of short-term outcome. *Surgery* 127: 276-283.
14. Gilbert AI and Felton IL (1993) Infection on inguinal hernia repair con14. sidering biomaterials and antibiotics. *SurgGynecol* 117: 126-130.
15. Jacek Szopinski, Stanislaw Dabrowiecki, Stanislaw Pierscinski, Marek15. Jackowski, Maciej Jaworski, et al. (2012) Desarda Versus Lichtenstein Technique for Primary Inguinal Hernia Treatment: 3-Year Results of a Randomized Clinical Trial. *World J Surg* 36: 984-992.
16. S M Situma, S. Kaggwa, N.M. Masiira, S.K. Mutumba (2009) Com16. parison of Desarda versus Modified Bassini inguinal Hernia Repair: A Randomized controlled trial. *East Cent. Afr. j. surg* 14:70-76.
17. Manyilira W, Kijambu S, Upoki A, Kiryabwire J (2012) Comparison 17. of non-mesh (Desarda) and mesh (Lichtenstein) methods for inguinal hernia repair among black African patients: a short-term double-blind RCT. *Hernia* 16: 133-144.
18. Yousset T, El-Alfy K, Farid M (2015) Randomized Clinical trial of pri18. mary inguinal hernia. *Int J Surg* 20: 28-34.
19. Dieng M, Cisse M, Seek M, Diallo FK, Tourè AD, et al. (2012) Cure 19. des hernies inguinales simples de L' adulte pastie avec L' aponèurose du grand oblique: Technique de Desarda. e-mèmoires de L'Académie Nationale de Chirurgie 11: 069-074.
20. Jianxin Z, Dong JW, Zhiyong Z (2013) Desarda inguinal hernia repair 20. and synthetic patch (open VS TEP) hernia repair comparative study. *J Chinese Her and abdominal Surg* 7: 559-563.
21. Lòpez Roduìguez PR, Pol Herrera PG, Leòn González OC, Cruz Alon21. so JR, Rodríguez Blanco HS (2013) A Randomized Trial Comparing Lichtenstein repair and no mesh Desarda repair for inguinal Hernia: A Study of 1382 patients. *East Cent Afr J Surg* 2013.
22. Stephen JN and Bruce T (2013) Abdominal wall, hernia and hernia and umbilicus, 22. Bailey and Love's; Short practice of surgery; 26th edn 2013: 957-958.
23. Szopinski J, Dabrowiecki S, Pierscinski S, Jackowski M, Jaworski M, 23. et al. (2012) Desarda Versus Lichtenstein Technique for Primary Inguinal Hernia Treatment: 3-Year Results of a Randomized Clinical Trial; *World J Surg* 36: 984-992.
24. Faruquzzaman, Kumar Mazumder S, Mozammel Hossain S (2016) 24. Dinaipur Med Col J 2016 9: 194-201.
25. Lòpez Rodríguez PR, Danta Fundora LM, Leòn González OC, Satorre Rocha JA, Garcia Castillo E, Durades Casanova A, Pol Herrera P. A Randomized Trial Comparing Modified Desarda Repair No Mesh and Lichtenstein Repair for Inguinal Hernia (A study of 1113 Patients). *Journal of Surgery* 2018; Vol 2018(07): J surgery an open access journal.
26. Lopez Rodríguez PR, Leòn González OC, Satorre Rocha Pol Herrera P, Garcia Castillo E, Durades Casanova A, Danta Fundora LM. A Randomized trial Comparing Desarda repair no Mesh and Lichtenstein repair for inguinal hernia (A study of 2225 patients). *Biomedical journal of Scientific & Technical Research*. 2018; Vol 6(4) <https://biomedica.us/submit-manuscript.php>.

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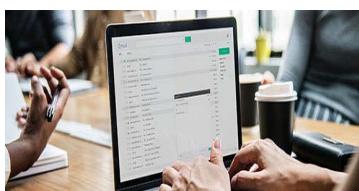
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17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not 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 through 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:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

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



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.



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.

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BY GLOBAL JOURNALS

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| Topics | Grades | | |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| | A-B | C-D | E-F |
| <i>Abstract</i> | 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 |
| <i>Introduction</i> | 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 |
| <i>Methods and Procedures</i> | 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 |
| <i>Result</i> | 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 |
| <i>Discussion</i> | 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 |
| <i>References</i> | Complete and correct format, well organized | Beside the point, Incomplete | Wrong format and structuring |



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