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CEP'S SUBSTANTIATED OPINION

RESEARCH PROJECT DATA

Research Title: EVALUATION OF RESPIRATORY MUSCULATURE STRENGTH IN PRE-OPERATIVE HEPATECTOMY OPERATION AND POST-OPERATIVE INSPIRATORY MUSCULATURE TRAINING.
Researcher: Marcelo Gustavo Pereira
Proponent Institution: Clinics Hospital of the UNICAMP
Main Sponsor: Own financing
OPINION DATA
Opinion Number: 2.748.781
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To Editorial Boarding,

This document certifies that the project presented below was approved by the Local Human Research Ethics Committee (Comitê de Ética em Pesquisa - CEP, State University of Campinas - Unicamp) and the National Commission on Ethics in Research (Comissão Nacional de Ética em Pesquisa - CONEP, Ministry of Health - Federal Government, Brazil) in its last version, on July 1st, 2019.

CAMPINAS, October 11th, 2022.

Signed by:
Renata Maria dos Santos Celeghini
(Coordinator)

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PROJECT PRESENTATION:

Liver neoplasms can be of primary or secondary origin. Among the primary ones, the main one is hepatocarcinoma or hepatocellular carcinoma (HCC) being the most frequent occurring in more than 80% of cases, there is also cholangiocarcinoma that affects the bile ducts (responsible for 5% of cases and usually occurs between the 6th and 7th decade of life, due to infestation by a trematode (clonorchis sinensis), common in Asian and African countries, the angiosarcoma that affects blood vessels (has carcinogenic potential due to chemical substances such as vinyl chloride, inorganic arsenicals and othorotrast (a solution of thorium dioxide) and hepatoblastoma which is described in children. Hepatic metastases (including solitary and multiple metastases) are common in patients who have some type of neoplasm, the most common being pancreatic carcinoma, colorectal carcinoma, stomach carcinoma, breast carcinoma, esophageal carcinoma, lung carcinoma and the carcinoid tumor. Risk factors for HCC have been identified, including peptic lo hepatitis B virus (HBV), chronic hepatitis C virus (HCV), hereditary hemochromatosis, liver storage diseases, alcoholism, non-alcoholic steatohepatitis and cirrhosis of another etiology. The American Association for the Study of Liver Diseases (AASLD) guideline guides screening with ultrasound every six months for patients at risk of developing HCC such as chronic carriers of hepatitis B and C virus and patients diagnosed with cirrhosis of any kind. etiology.

Hepatocarcinoma is the sixth most common tumor in the world and its incidence and risk factors are highly variable, being three times more common in men than in women and affecting individuals with a mean age of 64 years. Cirrhosis has been considered a pre-neoplastic condition for the development of HCC. The world incidence of HCC differs according to the different hepatitis viruses, in the United States, Europe and Japan being caused by the hepatitis C virus and in Asia and Africa by the hepatitis B virus, with high mortality worldwide, with an estimate of 600,000/year. In Brazil, the incidence of HCC shows etiological predominance due to liver cirrhosis and hepatitis C virus. Dividing by geographic regions, in the South and Southeast the predominant etiological factor was hepatitis C (HCV) and B (HBV) viruses, representing 60% of cases , North and Northeast by HCV and HBV corresponding to 50% of cases and Midwest by HBV. The total HCC ranges from 3.3% to 6% per 100,000 people/year, with a mortality rate between 3.6% to 6% per 100,000 people per year. There are several modalities for the treatment of HCC, including transplantation liver, surgical procedures, radiofrequency ablation, chemoembolization, chemotherapy and targeted therapies. Treatment will depend on the degree of hepatic dysfunction presented. Hepatectomies have become a safe surgical option over time, due to the detailed study of the hepatic anatomy, imaging tests, improvement of surgical techniques, patient evaluation, pre and postoperatively with a multidisciplinary team6. Hepatic neoplasms can be classified into benign and malignant, and both can propose resection. The benign ones are hemangiomas, adenomas and focal nodular hyperplasia. They

are usually asymptomatic, being opted for resection when they become symptomatic. The malignant ones are represented by primary and secondary neoplasms, among the primary is HCC with 70-85% of cases and requires surgical treatment. In primary liver tumors, surgical treatment is the most indicated, with the absence of distant metastases, and in metastatic liver tumors in which the primary lesion has been resected or can be resected in a curative manner. The amount of remaining parenchyma should be around 10% of body weight and the patient's clinical status is what elects the resection operation. In patients with liver cirrhosis, only those classified with CHILD A (initial cirrhosis) will be eligible for safe liver resection. Resection may be required in both benign and malignant liver lesions. Benign lesions are usually asymptomatic and their resection occurs only when they become symptomatic, whereas adenomas have a high risk of complications and require excision even in the absence of symptoms. Of the malignant tumors, hepatocellular carcinoma requires surgical treatment. Contraindications vary according to the amount, size and location of the nodules, patients who present with multifocal lesions related to diseases that limit the liver, presenting neoplasm of vascular branches or biliary structures that limit resection with adequate safety margin, size, quantity and location of the nodules. Therefore, alternative treatments should be chosen. Open hepatectomy is a surgical incision made across the upper part of the abdomen, following the curvature of the ribs. It can be bilateral subcostal for larger resections or just with left enlargement for smaller resections, if the mass to be sectioned is very large, the abdomen and thorax can be accessed at the same time as an anterolateral thoracotomy associated with median laparotomy or thoracophrenolaparotomy. Expansion of the resection depends on liver function and there is no cirrhosis. Large liver resections should be performed when lesions are larger, as there is an increase in progression-free survival, and up to two-thirds of the liver can be removed. The operation lasts about 3 to 4 hours, the patient must stay in the ICU for at least 24 hours to monitor bleeding and liver function, returning to the ward when clinically stable, and may remain hospitalized for up to 10 days. After surgical removal of part of the liver, the organ begins to regenerate within 48 hours and reaches near-normal size in 3 to 4 weeks, and function returns to normal in 6 to 8 weeks. Some advantages of liver resection that can be mentioned are: immediate availability in specialized centers; low risk in well-selected patients; accurate histological evaluation; overall survival rates comparable to intention to transplant; possibility of salvage liver transplantation in cases of recurrence, as long as patients are closely monitored to diagnose recurrences early and to reduce costs on the overall economy of liver transplantation15. The most common surgical contraindications are: patients with compromised cardiopulmonary function, severe malnutrition, impaired liver function, extrahepatic metastatic disease and invasion of the bifurcation of the portal vein or the trifurcation of the hepatic veins13. The most common clinical complications are pneumonia, deep vein thrombosis, pulmonary thromboembolism and liver failure. Regarding surgical complications, bleeding and leakage of bile from the surface of the resected liver may occur. When undergoing upper abdominal surgery, there

may be postoperative complications that are not uncommon, with changes in respiratory mechanics, hematosis and in the pulmonary defense mechanism, allowing the emergence of pulmonary complications. The implication of lung function after upper abdominal surgery decreases Functional Residual Capacity (FRC), Forced Vital Capacity (FVC) and Partial Oxygen Pressure. These are changes resulting from improper lung insufflation, which due to a superficial breathing pattern and the anesthetic action of the immediate postoperative period.

Short-term diaphragmatic dysfunction, prolonged dorsal decubitus and pain at the operated site favor a decrease in (FRC). close to the diaphragm, generating changes in the biomechanics of the region. Complicating morbidity, pain plays an important role in impeding the progress of therapy and procrastinating hospital discharge. In upper abdominal surgery, a reduction in vital capacity (VC) can be expected. The height of diaphragmatic dysfunction is the cause of the main reduction in respiratory muscle strength, occurring after surgery, returning to preoperative values around seven to ten days. Through the values obtained at the bedside of the diaphragmatic dysfunction, the maximum inspiratory pressure (PImax) is highlighted. To obtain these values, the manovacuometer is used, so the patient needs to be seated, next to a nose clip, using a recessed rubber mouthpiece connected to the manovacuometer. When measuring MIP, the patient is instructed to exhale from residual capacity and perform a maximum inspiration sustained for at least two seconds. In the MEP measurement, the orientation is from a deep inspiration until the total lung capacity expelling until the residual capacity with a maximum impulse performing three repetitions with one-minute intervals in both techniques, so the best result is obtained. To obtain the values of an individual's MIP and MEP within the normal range, an equation predicted for men and women is found in the literature. For men: MIP: y = 0.80 x age + 155.3 MEP y = 0.81 x age + 165.3. And for women: MIP y = 0.49 x age + 110.4 MEP y = 0.61 x age +115,620,21. The concepts of respiratory muscle weakness and fatigue can be defined by carefully measuring MIP and MEP as aforementioned. Muscle fatigue is understood as the inability of the muscles to generate force to maintain activity for a certain time, being reversible with rest; weakness is the inability of the musculature to maintain activity for a certain time, however, it is not reversible with rest. Studies have described that patients with reduced values of maximal respiratory pressures without significant improvement after inspiratory muscle training (IMT) had a higher risk of developing postoperative pulmonary complications. The literature has shown that training the respiratory muscles in the postoperative period increases inspiratory and expiratory muscle strength, in addition to favoring the effectiveness of coughing, preventing atelectasis. The concepts of respiratory muscle training are the same as for other muscles: overload, specificity and reversibility. As for overload, a muscle to be trained must receive a high load, with quick and brief repetitions. For resistance training, the load should be lower, with more repetitions.

For training to be specific, the activity must directly involve the muscles to be trained. For respiratory muscle training, the best results are obtained with

specific training. Reversibility refers to the disappearance of training effects if training is stopped. Training can be specific to strength, endurance, or speed, but really, there is always a mix of effects. In resistance training it is possible to increase strength, as strength and endurance are strongly correlated. Strength training results in an increase in the size and number of myofibrins in white fibers (IIa and b), which generates hypertrophy. Ventilometry is a low-cost and simple resource, widely used by physical therapists to recognize changes in ventilatory mechanics, capable of defining volumes and vital capacity, which corresponds to approximately 80% of total lung capacity. The values achieved in the pulmonary function test are measured with those of healthy people. Conventional physical therapy is of great importance in the postoperative period of hepatectomy, reducing pulmonary complications, reducing hospital stay and reducing costs. Being a relevant procedure in the patient's recovery, from an appropriate positioning in the bed such as sitting, bronchial hygiene maneuvers such as vibrocompression, increased expiratory flow (EFA), huffing and coughing, preventing the accumulation of secretion in the lungs and increasing oxygenation, suction of the orotracheal tube, tracheostomy, oral and nasotracheal cavity and lung re-expansion maneuvers with directed flow, compression/decompression and respiratory incentive. The TMI can be performed using the Powerbreathe® device, an electronic device used to strengthen the respiratory muscles, with the nose obstructed by a nose clip and a mouthpiece where the patient performs a sequence of inspirations in series of repetitions, with the principle of training resisted by integrating into a flexible or automatic load fully embraces the capabilities of an increasing TMI. When performing IMT with Powerbreathe®, the forced load on the respiratory muscle can be varied. Normally, this load can be fixed by means of an initial recording, or actively with electronic regulation.

RESEARCH PURPOSE:

GENERAL OBJECTIVE: To compare the assessment of respiratory muscle strength in the preoperative period of open hepatectomy and the training of the inspiratory muscles in the postoperative period using the Powerbreathe® device.

SPECIFIC OBJECTIVE: To assess maximal inspiratory pressure (PImax) and maximal expiratory pressure (MEP) using a manovacuometer in the preoperative period and on the first and fifth postoperative days; To assess tidal volume and vital capacity using a ventilometer in the preoperative period, first and fifth postoperative day; Compare with the control group if the patients who obtained respiratory muscle training through the intervention with the Powerbreath® device had better measurement of respiratory pressures and fewer complications in the postoperative period; Follow the general condition of the patient, hemodynamics , complementary and laboratory tests;Record the length of stay of patients after the surgical procedure;Relate types of liver neoplasms with the surgical extension;Evaluate the impact of hepatectomy surgery on respiratory muscle strength.

ASSESSMENT OF RISKS AND BENEFITS:

According to the researchers the risks: This research has no foreseen risks, it is expected that the patient and/or guardian will not suffer discomfort, risks or side effects in the participation of the same. And if this occurs, the patient and/or guardian are free to disconnect at any time without any loss, fine or damage. It may happen that when performing the powerbreathe®, the participant experiences pain. If the pain medication is not optimized, the training will be stopped and the medical team will be discussed to optimize the medication, if the patient maintains a complaint, the service will be interrupted. Benefits: The patient and/or guardian are assured that they have not received any financial compensation related to their participation in this study. As well as, they will not have any personal expenses during the study, the development of this research will be carried out in the routine of the participant or responsible. of open hepatectomy.