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NERRATIVE REVIEW **INTENSIVE CARE**

The effect of a combination of functional electrical stimulation and cycle ergometer (FES-cycling) on physiological changes and functional ability in patients with ICU-acquired weakness

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ABSTRACT

Intensive care unit-acquired weakness (ICU-AW) is the most common complication found in the intensive care unit (ICU) patients, especially those on prolonged use of mechanical ventilation (MV). It is known to cause poor long-term outcomes, and early rehabilitation (ER) intervention has been proved to be useful in improving muscle strength, physical function, and quality of life of ICU survivors. Several obstacles, such as patients' medical condition and limited availability of equipment or trained personnel, interfere with ER. Passive ER including functional electrical stimulation (FES) and cycling were found to be effective. The combination of FES with a cycle ergometer (FES cycling) can be implemented, but research on using this modality in the ICU is still limited. This review aimed at providing information on the use of FES cycling in ICU patients to explain its effect on physiological changes and functional abilities. The physiological effects of FES cycling are obtained through local metabolic changes in muscles due to FES and increased cardiovascular responses due to muscle contraction during cycling. Its effects on muscle strength, cross-section area, days free of MV, mobilization, cognitive ability, delirium, and quality of life were positive, and only rarely adverse events occurred during the intervention. To conclude, the use of FES cycling in the prevention and treatment of ICU-AW can be considered since this modality causes positive physiological effects and has proven safe.

Abbreviations: EM – Early Mobilization; ER- early rehabilitation; FES - functional electrical stimulation; ICU-AW - Intensive Care Unit-Acquired Weakness; MV - mechanical ventilation; NMBA - neuromuscular blocking agents; PICS - post-intensive care syndrome; NMES - neuromuscular electrical stimulation;

Key words: Electrical Stimulation; Intensive Care Unit; Muscle Contraction; Muscle Strength; Quality of Life

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1. INTRODUCTION

Intensive care unit-acquired weakness (ICU-AW) is the most common complication found in intensive care unit (ICU) patients, especially those with prolonged mechanical ventilation (MV). The incidence of ICU-AW in ICU patients is approximately 40%.[1,2] This incidence is increased in patients with sepsis, hyperglycemia, users of neuromuscular blocking agents (NMBA), corticosteroids, and long-term use of MV.[3] The presence of ICU-AW causes difficulty in weaning from MV which further worsens muscle weakness.[4] ICU-AW also causes poor long-term outcomes, especially contributing to the occurrence of post-intensive care syndrome (PICS) which consists of physical, cognitive, and psychological dysfunctions that are found for years after being discharged from the ICU.[5,6]

Early rehabilitation (ER) intervention is known to be a useful intervention to prevent the occurrence of ICU-AW and improve muscle strength, physical function, and quality of life (QoL) of ICU survivors.[5-7] ER is associated with shorter use of MV and length of ICU and hospital stay.[5,7] Some of the modalities used for ER programs in the ICU include passive exercise, neuromuscular electrical stimulation (NMES), cycle ergometer, active exercise, and early mobilization (EM).[5,6]

Several obstacles were encountered in ER interventions because the patients' medical conditions were unstable so they could not actively participate in the ER program. In addition, the limited equipment and personnel in the ICU make it difficult to implement an ER program.[8-10] Functional electrical stimulation (FES) and cycle ergometers are modalities used to increase muscle mass and strength, physical function, and other ICU outcomes.[8,11]

The use of FES and cycle ergometer separately in ICU patients is effective and does not cause significant adverse events.[12,13] The combination of FES with a cycle ergometer (FES cycling) is a modality that can be implemented in an ICU with limited staff. This intervention was developed to improve ICU outcomes,[9,14] unfortunately, research on the use of this modality is still limited.

Objective of the study

This review was written to provide information on the use of FES cycling in ICU patients based on previous studies. The focus of discussion in this review is the use of FES cycling in ICU patients and its effect on physiological changes and functional abilities.

2. METHODOLOGY

Articles published in the last 10 years were searched using PubMed and Google Scholar databases. Keywords used were "FES-Cycling and ICU", "FES-Cycling and mechanical ventilation", "Functional electrical stimulation and cycling", "Electrical stimulation and ICU", "Electrical stimulation and mechanical ventilation", "Functional Electrical Stimulation and ICU", "Cycle ergometer and ICU", "Passive early rehabilitation", "Early rehabilitation in ICU", and "Early rehabilitation and mechanical ventilation". Citations and references of articles found by keywords were also explored. Articles that were not available in full text and not written in English were excluded. Original articles were extracted to explore more about the dose and physiological effects.

3. RESULTS

Twenty-six of the published studies were found and used to explain sub-topics. Thirteen of these were experimental studies and 13 were review articles.

4. DISCUSSION

4.1. Objectives, Indications, and Contraindications of FES cycling

FES cycling is one of the modalities used in ER programs given to ICU patients.[15] FES is a device consisting of a stimulator that uses a battery connected by a cable to an electrode and an external trigger to synchronize muscle contractions with functional activity.[16] Cycling is a type of exercise that uses a stationary bicycle with an automatic mechanism that can change the muscle work performed by the patient which can be used passively or actively.[6] FES cycling uses a computer-directed electric current delivered through a transcutaneous electrode that directly activates muscle contraction.[17]

Several previous studies have provided FES cycling to improve cardiovascular response, prevent atrophy, and increase muscle activity in ICU patients.[15,18] This intervention is also known to improve cardiorespiratory fitness, insulin sensitivity, bone density, muscle properties, intramuscular blood flow, and muscle strength or endurance.[17,19,20]

Fossat et al. provide FES cycling in ICU patients who require more than 48 h of care.[18] Parry et al. gave FES cycling within 96 h of ICU care and continued daily until discharge from the ICU.[21] Other studies provided this intervention in patients who were intubated for at least 24 h, patients on MV with adequate cardiac reserve as demonstrated by resting heart rate variability < 20%, patients with systolic blood pressure 90-180 mmHg, normal electrocardiography, saturation peripheral oxygen > 90%, the fraction of inspired oxygen < 60%, respiratory rate < 25/min, hemoglobin > 7g/dl, platelets >20,000/mm^3, and no diagnosis of sepsis.[19]

Conditions that cause FES cycling are not given include patients with an acute cerebral disease requiring at least 72 h of sedation, acute polyradiculoneuropathy, myasthenia gravis, advanced dementia, deep vein thrombosis or pulmonary embolism treated for less than 48 h, patients using a temporary pacemaker or implantable cardioverter defibrillator, patients who have experienced cardiac arrest or have experienced cardiac arrest, have an acute fracture, amputation or weakness of the lower limbs, have contraindications to standing or transfer to a chair, patients who are candidates for palliative care, patients with medically unstable conditions, have contraindications to electrical stimulation (ES) or leg cycling, and pregnancy.[18,22] The FES cycling was also not given to patients who were unable to walk without a walker before admission to the ICU, pregnant patients, with body mass index > 35, diagnosed with vascular disease, and skin lesions at the electrode attachment site.[19]

4.2. Physiological Effects

The physiological effects of FES cycling include increased cardiac output, oxygen consumption (VO_2), and muscle metabolism through a decrease in oxyhemoglobin and an increase in deoxyhemoglobin. Physiological effect is obtained through an increase in local metabolism in the muscle due to ES and an increase in metabolic energy requirements and cardiac output due to increased cardiac activity and muscle contraction during cycling. Cardiovascular response after this FES cycling was not found in passive cycling.[15,23]

The metabolic efficacy of FES cycling is very low at about 5%-10% when compared to active cycling at around 25%-40%. This is caused by the pattern of muscle activation. In active cycling, large muscle groups are activated simultaneously compared to smaller units.[17, 24] Cycling can trigger a metabolic shift to anaerobic with a mild increase in lactate production which may be due to impaired microcirculation during contraction or due to an imbalance between glycogenolysis and pyruvate oxidation.[17,25] There is no data on the effect of FES on amino acid metabolism as found in active cycling. FES cycling is given to ICU patients, especially for patients with marked protein catabolism and a poor ability to clear lactate from the systemic circulation.[17]

4.3. The Rationale for FES Cycling

The consequences of ICU care are the occurrence of ICU-AW is characterized by weakness and loss of muscle mass (atrophy).[2-4,26] This situation has an impact on short-term and long-term outcome complications that affect the patient's physical function and QoL.[4,11] Muscle atrophy and dysfunction occur rapidly in critically ill patients.[17] Factors resulting from ICU care such as prolonged use of MV, use of sedative drugs, corticosteroids, and neuromuscular blocking agents as well as sepsis led to a catabolic state.[3,4,7] Catabolic state causes a decrease in anabolic hormones and an increase in catabolic hormones which further results in an imbalance between muscle protein synthesis and degradation. In critically ill patients, muscle atrophy results from the loss of myosin and the protein myoglobin.[3,4] Immobilization causes atrophy to be more pronounced in ICU patients which in turn causes weakness.[4]

The incidence of ICU-AW with muscle weakness can be prevented by giving an ER program as early as possible in the ICU, which even can be initiated when the patient is unconscious or sedated.[4,27,28] Various ER modalities are known to play a role in achieving this goal such as passive exercise, use of NMES or FES modalities, and passive or active cycling.[4,27]

NMES in ICU patients has been shown to maintain muscle mass and prevent the occurrence of ICU-AW.[9] FES and NMES interventions are modalities that use the principle of ES. The difference between these two modalities is that in FES there is a functional pattern of muscle recruitment because this modality stimulates muscles in the same way as normal muscle contraction during conscious functional activity. Another method for muscle recruitment with a functional pattern is to use cycling.[11,29,30]

Leg cycling in mechanically ventilated patients is associated with improved physical function and QoL.[5] In patients with sepsis who received cycling, the muscle fiber cross-section did not decrease at 7 days of treatment. It was also reported that in patients who received cycling 3 days after ICU treatment, there was a higher increase in muscle strength scores at the time of discharge from the ICU.[22]

EM is an intervention that has been shown to prevent the development of ICU-AW.[7,17] EM is only feasible in conscious and cooperative patients so a reduction in the sedation dose is required to facilitate it. In addition, for EM, adequate pain management is needed as also early recognition and management of delirium. There is also a need for the availability of sufficient equipment and personnel to facilitate EM. Therefore, there is a need for techniques or modalities that can be applied to groups of patients who have difficulty actively participating in EM programs.[6,7]

The use of modalities such as FES and exercise with a cycle ergometer can be initiated passively and gradually increased to active exercise. Bed cycling in mechanically ventilated patients is associated with improved physical function and QoL.[5,7] FES cycling is thought to affect muscle strength and physical function not only upon discharge from the ICU but also upon discharge from the hospital.[11]

In patients who received a bed cycling 3 days after ICU treatment, there was a higher increase in muscle strength scores at the time of ICU discharge.[22] Compared to ambulation, bed cycling is easier to apply in critically ill patients. Adverse events resulting from this intervention were found to be rare. NMES interventions can maintain muscle mass and prevent ICU-AW, but it is difficult to induce strength gains with NMES alone.[9]

The use of cycling alone does not effectively increase muscle metabolism, whereas the use of FES affects local metabolism but not the cardiovascular system. The lack of effect on cardiac output explains why there is no change in functional capacity during FES administration.

The FES cycling that induces muscle contraction can be used to provide an early, higher-intensity rehabilitation program for sedated patients who cannot get out of bed.[15] FES cycling can also help to provide exercise before the patient can actively participate in the mobilization program and during the acute phase.[7,17] The use of FES cycling in critically ill patients has also been shown to be feasible and safe.[21]

4.4. Therapeutic Doses of FES Cycling in ICU Patients

Previous studies provided FES cycling with varying therapeutic doses and no standard protocol of intervention was found. A summary of the therapeutic dose given based on previous studies is described in Table 1.

4.5. Adverse Events

Data on adverse events during the use of cycling in ICU patients are still limited. Waldauf et al. in their study did not find any disturbances in cardiorespiratory function or other disorders. In this study, there were also no patients who needed immediate intervention and changes or additional drug doses.[31] In line with the research of Waldauf et al., Gojda et al. found that all study subjects were able to complete the exercise protocol without any adverse events.[17] Berney et al. in their study also did not find any serious adverse events. Complaints that occurred during therapy were experienced in both groups and could be resolved by temporarily discontinuing therapy without any clinical consequences.[32] Another study by Parry et al. found no major adverse event and only one minor adverse event was found. The patient experienced a transient desaturation of 86% over 1 minute and required a temporary increase in FiO_2 from 0.4 to 0.6 over 1 h.[21]

The frequency of clinically significant adverse events (> 1 event occurring during the mobilization session and requiring therapeutic intervention beyond simple measures) occurred between the intervention group receiving the FES cycling and the control group receiving standard care. Among the patients in the intervention group, 2 adverse events were directly related to the mobilization session, namely skin allergies due to pads and extubation during cycling requiring reintubation. This event was not found in the control group.[18]

Efforts made to reduce the possibility of adverse events in the provision of FES cycling are monitoring vital signs during all rehabilitation sessions and resetting the workload by increasing or decreasing the load if there are changes in heart rate and blood pressure > 10% and desaturation < 95%.[9]

4.6. Effects of FES Cycling on Physiological Changes

Cycling intervention affects physiological functions of the body through several mechanisms including metabolic changes that cause lactate production, balance of oxygen consumption and transport, and changes in physiological parameters of the cardiovascular and respiratory systems.[15,17] The changes that occur after the administration of FES cycling begin with changes in anaerobic metabolism that cause a mild increase in arterial lactate levels which in turn leads to fatigue.[17]

A study comparing the metabolic response of skeletal muscle during FES cycling versus bed cycling active cycling led to an increase in lactate production without signs of imbalance in oxygen consumption and delivery. This happens because at low-intensity exercise there is an increase in lactate production in type 2b muscle fibers and lactate consumption in type 1 muscle fibers. In general, high-intensity exercise will cause an increase in lactate production accompanied by an imbalance in oxygen consumption and delivery which causes oxidative stress.[17]

Oxidative and nitrosative inflammatory processes are potential causes of ICU-AW [*Nitrosative stress refers to the joint biochemical reactions of nitric oxide (NO) and superoxide (O_2–) when an oxygen metabolism disorder occurs in the body*]. One study found that the administration of FES and cycle ergometers was effective in reducing nitric oxide levels one hour after administration in ICU patients. This suggests that these two therapies can reduce nitrosative when administered separately. This study did not get the same effect after the administration of FES in combination with a passive cycle ergometer. Serum cytokine levels did not change with FES and cycle ergometers unless there was a decrease in tumor necrotizing factor a (TNF-α) in the group that received cycle ergometer passive results of this study was different from previous studies which found a decrease in cytokine levels (interleukin 6 and TNF-α) after administration of FES.[19]

Medrinal et al. found that FES cycling increased cardiac output and cardiorespiratory physiological responses and decreased oxyhemoglobin in muscles. The increase in cardiac output with the use of FES cycling is about 15% (1 L/min). An increase in heart rate indicates that there is an increase in stroke volume which reflects an increase in global heart activity.[15] Increased cardiac output was not found with the use of other modalities such as passive range of motion of the limbs, passive cycle ergometers, and electrical stimulation of the quadriceps muscles. This is because low-intensity exercise will only induce low-level muscle work. Cardiovascular and respiratory

Table 1: Therapeutic Doses of FES Cycling in ICU Patients

Research	Therapeutic Doses
Medrinal et al. (2018)[15]	● **The duration** FES cycling was 10 minutes. This intervention was combined with passive lower limb mobilization, electrical stimulation of the Quadriceps, and cycle ergometer for 10 minutes each with a 30-minute rest interval between each intervention. ● **Intensity** 1. The intensity of the electrical stimulation is modulated until muscle contraction is palpable. 2. The pedaling frequency is set at 20 revolutions per minute. ● **Mode** 1. Electrical Stimulation was rectangular, intermittent, and bidirectional without a ramp. The wavelength of 300 s and a frequency of 35 Hz. Two electrodes measuring 5x9 cm are positioned on either side of the leg on the Quadriceps to stimulate the entire muscle. 2. Cycle ergometer: during the use of the cycle ergometer, the stimulator is computer-controlled so that muscle contraction is induced at the correct pedal angle during knee extension.
Fossat et al. (2018)[18]	● **Frequency** FES cycling is given every weekday and is combined with standard early rehabilitation starting with passive leg ROM exercises followed by passive or active exercises until mobilization. ● **Duration** Quadriceps muscles for 50 minutes with a stimulator consisting of 4 channels. Exercise with a cycle ergometer was given for 15 minutes on the same day.
Berney et al. (2020)[32]	FES cycling for 60 minutes per day, ≥5 days per week combined with standard care.
Gojda et al. (2019)[17]	● **Duration** Cycle ergometer is given for 30 minutes in the supine position and consists of 3x10 minute interval training. ● **Mode** 1. Cycle ergometer: workload 10 W (13 revolutions per minute with a load of 7 N/m), 25 W (31 revolutions per minute with a load of 7.6 N/m), and 50 W (35 revolutions per minute with a load of 13.4 N /m). The exercise begins with a warm-up for 5 minutes. 2. Electrical stimulation: After 5 minutes of passive warm-up with a workload of 25 revolutions per minute, the target speed is changed to 30 revolutions per minute. Stimulation is started and increased in increments of 1% per second to reach an amplitude of 25 mA, then the stimulation is increased steadily to reach the maximum intensity that the patient can tolerate.
Woo et al. (2018)[9]	● **Duration** 1. Bed cycling: intervention bed cycling is given for 20 minutes. After bed cycling, the patient was given a rest for 10 minutes. 2. Electrical stimulation: FES intervention was given for 20 minutes. ● **Intensity** starts with passive mode with a speed of 20 revolutions per minute, then the load is given by adjusting the cycle ergometer until the patient shows signs of fatigue. During weight training, it is maintained stable or does not change heart rate and blood pressure >10% and desaturation <95%. ● **Mode** 1. Bed cycling each session starts with a warm-up with a cycle ergometer for 1 minute at a speed of 20 revolutions per minute. Exercise is continued with passive/active assistive or cycling for 19 minutes depending on the patient's level of participation. The exercise is completed after a 30-second cool-down period. 2. Electrical stimulation: Electrical stimulation was given with 4 electrodes at the lateral border of the Quadriceps wave biphasic symmetric frequency of 35 Hz, a duty cycle of 10 seconds on and 12 seconds off, and a pulse time of 250 seconds. The threshold of stimulation is at the point where muscle contraction is seen.

Table 1: Therapeutic Doses of FES Cycling in ICU Patients (Contd)	
Research	**Therapeutic Doses**
Parry et al. (2014)[21]	● **Duration** Intervention cycling is given for 20-60 minutes, 5 days a week ● **Intensity** The intensity is given until contractions are seen and muscle contractions are assessed every 5 minutes. The intensity is increased until it reaches a maximum amplitude of 140 mA. The patient is motivated to actively participate in the exercise and the workload is gradually increased. ● **Mode** Electrodes are placed on the large muscles of the lower leg including the quadriceps, Hamstring, gluteal and calf muscles. The current used is an alternating monophasic rectangular waveform duration pulse of 300-400 microseconds and the frequency is 30-50 Hz.

parameters such as respiratory rate, mean arterial pressure, pulmonary artery systolic pressure and tricuspid valve systolic excursion in the annular plane also increased with FES cycling.[15] The biggest change in cardiovascular parameters found in other studies was a heart rate variation of 20-40 beats per minute during exercise. Although during exercise there was a decrease in heart rate, there was no difference in heart rate and respiratory rate at the beginning of the exercise and 30 minutes after exercise.[21]

4.7. Effect of FES Cycling on Functional Ability

Fossat et al. in their study assessed whether the combination of electrical stimulation of the quadriceps muscle and early in-bed cycling provided an additional benefit in increasing global muscle strength assessed on discharge from the ICU compared to a standard early rehabilitation program. In this study, there was no difference in the increase in global muscle strength as assessed by the medical research council at the time of discharge from the ICU.[18]

Another study assessed whether there was a difference in muscle mass and strength in ICU patients using mechanical ventilation after FES cycling and in-bed cycling. This study found that the cross-section of the rectus femoris and thigh circumference had a significant increase after the administration of the two interventions, but statistically, there was no significant difference between the two parameters.[9]

Berney et al. compared the effect of adding FES cycling to a routine rehabilitation program on quadriceps muscle strength at discharge and 6 months later. Their study found that the addition of FES cycling did not substantially increase muscle strength upon discharge from the hospital.[32] Waldauf et al. also found no difference in cross-sectional cross-section of the Rectus femoris and muscle strength at discharge between the groups given FES cycling compared to standard rehabilitation. This is because the control group that received the standard rehabilitation program was given the rehabilitation intervention earlier and at a higher dose than that given in previous studies.[31]

Previous studies also assessed the effect of FES cycling on days free from mechanical ventilation, mobilization, cognitive function, delirium, and quality of life.[18,21,32] There was no significant difference in the number of days free from mechanical ventilation on day 28 and there was no difference in the ICU mobility scale at the time of discharge from the ICU.[18] Research Parry et al. also found that recovery of functional status tended to be earlier and faster in the group given the FES cycling.[21]

Cognitive function 6 months after hospital discharge did not decrease with the addition of FES cycling to standard care.[19] The frequency of delirium was lower in the group of patients receiving the FES cycling compared to standard rehabilitation, although not statistically significant. The duration of delirium was significantly shorter.[21]

Research data on the effect of FES cycling on quality of life are very limited. Fossat et al. found that there was no significant difference in the quality of life at 6 months after discharge from the ICU between the groups of patients receiving FES cycling compared to standard rehabilitation.[18] Waldauf et al. also did not find a difference in the quality of life scores assessed by Short-form 36 items at 6 months between the group of patients who received FES cycling with standard care.[31]

Previous literature states that early rehabilitation interventions provided with the use of various physical modalities in the ICU can reduce physical and mental health complications that often occur in critically ill patients. The benefits of early physical rehabilitation include increased muscle strength, physical function, and quality of life, as well as reduced health care costs and length of hospital stay.[5] FES cycling as a form of an early rehabilitation program can be an option that can be considered, especially in patients who cannot perform active mobilization.[18]

5. CONCLUSION

FES cycling as a modality of ER program in the ICU aims to improve cardiovascular response, prevent atrophy, and increase muscle activity. This intervention is given to ICU patients who require treatment with or without mechanical ventilation for at least 24 h. Several conditions cause the FES cycling not to be given including conditions that cause the use of electrical stimulation and cycling contraindicated. The physiological effects of FES cycling are obtained through local metabolic changes in muscle due to electrical stimulation and increased cardiovascular response due to muscle contraction during cycling.

FES cycling affects physiological functions through metabolic changes that cause lactate production, balance of oxygen consumption and transport as well as changes in physiological parameters, cardiovascular and respiratory systems. Previous studies have found that FES cycling causes an increase in lactate production without an imbalance in oxygen consumption and delivery that causes oxidative stress. The FES cycling also did not cause changes in serum cytokine levels. Cardiac output increased significantly after the FES cycling. Research on the effect of FES cycling on physiological changes and functional abilities is still very limited. The effect of FES cycling on physiological changes showed varying results related to the increase in muscle strength and cross-section of the Quadriceps at the time of discharge from the hospital. The effect of FES cycling on days free of mechanical ventilation, mobilization, cognitive function, delirium, and quality of life also varied. Based on the physiological effects of FES cycling on physiological parameters and functional abilities and research evidence that adverse events occur in FES cycling are rare, FES cycling can be considered, especially in patients who cannot perform active mobilization.

6. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

7. Authors' contribution

AN is the sole author of this manuscript.

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