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Effect of vibration therapy on physical function in critically ill adults (VTICIA trial): protocol for a single-blinded randomised controlled trial

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ABSTRACT

Introduction Vibration therapy has been used as an additional approach in passive rehabilitation. Recently, it has been demonstrated to be feasible and safe for critically ill patients, whose muscle weakness and intensive care unit (ICU)-acquired weakness are serious problems. However, the effectiveness of vibration therapy in this population is unclear.

Methods and analysis This study will enrol 188 adult critically ill patients who require further ICU stay after they can achieve sitting at the edge of the bed or wheelchair. The sample size calculation is based on a 15% improvement of Functional Status Score for the ICU. They will be randomised to vibration therapy coupled with protocolised mobilisation or to protocolised mobilisation alone; outcomes will be compared between the two groups. Therapy will be administered using a low-frequency vibration device (5.6–13 Hz) for 15 min/day from when the patient first achieves a sitting position and onward until discharge from the ICU. Outcome assessments will be blinded to the intervention. Primary outcome will be measured using the Functional Status Score for the ICU during discharge. Secondary outcomes will be identified as follows: delirium, Medical Research Council Score, ICU-acquired weakness, the change of biceps brachii and rectus femoris muscle mass measured by ultrasound, ICU mobility scale and ventilator-free and ICU-free days (number of free days during 28 days after admission). For safety assessment, vital signs will be monitored during the intervention.

Ethics and dissemination This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital. Results will be disseminated through publication in a peer-reviewed journal and presented at conferences.

Trial registration number UMIN000039616.

Strengths and limitations of this study

- This randomised controlled trial is the first to evaluate whether vibration therapy can improve physical function and delirium in critically ill patients.
- The 15 min intervention is added to protocolised mobilisation from the start of sitting position onward till discharge from the intensive care unit.
- This trial will contribute evidence-based treatment data in using vibration therapy in critically ill patients, a population for which current data are insufficient.
- Limitations of this study are the short length of intervention and the use of vibration therapy added to protocolised mobilisation, not vibration therapy alone.

INTRODUCTION

There has been a decline in the mortality rate for critically ill patients by 35% over two decades.[1] However, survivors often experience prolonged impairment in their quality of life. In a study, one-third of septic patients were identified to have some type of psychological or physical dysfunction 6 months after discharge from the intensive care unit (ICU).[2] These conditions are referred to as post-intensive care syndrome (PICS), which encompasses prolonged physical, mental and cognitive dysfunction.[3] A significant cause of PICS is muscle weakness newly acquired in the ICU, which is termed as ICU-acquired weakness (ICU-AW). This condition is associated with prolonged physical dysfunction, which is observed in 40% of critically ill patients.[4]

Physical therapy is essential to prevent muscle weakness and delirium.[5 6] Mobilisation has been widely recognised to be important in critically ill patients; however, out-of-bed mobilisation is not widely practiced.[7] In a one-point prevalence study, 33% of mechanically ventilated patients were mobilised out of bed and 2% were ambulated, suggesting that active mobilisation is still infrequent in critically ill patients.[8] The barriers to mobilisation vary, such as very heavy medical staff workload, limited staffing and insufficient equipment.[9] The heavy workload of nurses hampers their active involvement in patient mobilisation,[10] and full-time physical therapists are still not common in several ICUs.[11] Because these human resources are often

limited, there is an urgent need for equipment and devices to support rehabilitation in the ICU.

Since 1960, vibration therapy has been used as an additional approach in passive rehabilitation.[12] This therapy generates vertical sinusoidal vibration. The transmitted vibration stimulates muscle spindles and produces muscle contractions. Studies have reported that vibration therapy improved physical function in both healthy individuals and patients with chronic disease.[13 14] A recent report documented that vibration therapy was safe and feasible in critically ill patients.[15] The device does not require patients' active cooperation and can be used passively. Because mobilisation for critically ill patients is often limited to sitting without standing or ambulating,[8] the device can contribute to maximising passive mobilisation.

The study hypothesis is that vibration therapy can improve physical function in critically ill patients. The primary objective is to investigate its effect on physical function measured at discharge from the ICU. The secondary objectives are to determine the effects of vibration therapy on muscle strength, muscle mass, mobility level, delirium and ventilator-free and ICU-free days (number of free days during 28 days after admission). This study will allow us to objectively analyse whether vibration therapy can improve physical functions and how it impacts clinical outcomes in critically ill patients.

MATERIALS AND METHODS

Study design and settings

In August 2020, the authors will initiate a single-blinded, randomised controlled trial at the mixed medical/surgical ICU of Tokushima University Hospital in Japan. The trial is expected to take 2 years to complete. This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital (approval number 3763). This study is based on the prospective, randomised, open-label, blinded endpoint study model and the standard protocol items: recommendations for interventional trials statement.[16 17]

Recruitment

All consecutive patients who meet the inclusion and exclusion criteria described in the following text will be enrolled in this study. At the time of enrollment, written informed consent will be obtained from patients or their authorised surrogate decision-makers. A model consent form used in this study is available in the online supplemental file 1.

Inclusion and exclusion criteria

The study will enrol consecutive critically ill patients aged ≥18 years who require further ICU stay after being eligible for study participation (figure 1). Patients will be eligible when they can achieve sitting at the edge of the bed or wheelchair with or without mechanical ventilation. The study will exclude patients based on the consensus for early mobilisation in the Japanese Society of Intensive Care Medicine (JSICM) as follows[18]: (1) no permission from the primary physician; (2) excessive agitation (Richmond Agitation-Sedation Scale (RASS) ≥2); (3) impaired consciousness (RASS ≤−3); (4) unstable vital signs requiring circulatory support devices, such as intra-aortic balloon pump; (5) sustained low blood pressure even with the use of catecholamine; (6) dynamic blood pressure change after body position change; (7) risk for rupture in untreated aneurysms; (8) uncontrolled pain; (9) uncontrolled intracranial pressure ≥20 mm Hg; (10) unstable phase in the head or cervical spine injury; (11) metal implants or unstable bone fractures in the extremities or spine; (12) active bleeding; (13) insufficient stabilisation or length of catheters; (14) insufficient staffing and (15) no consent from patients or surrogates.

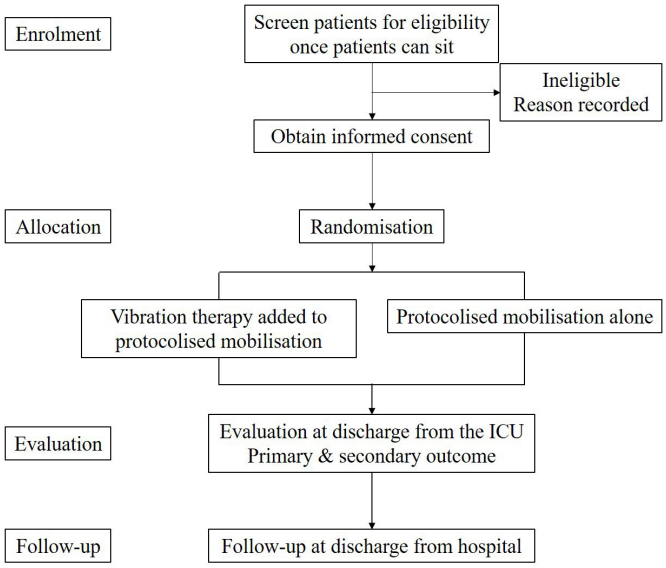

Figure 1 Flow chart of study protocol. ICU, intensive care unit.

Withdrawal from the study

Patients can withdraw from the study at any time, which will not affect the medical care they are receiving on withdrawal. The research team will stop the intervention and consider withdrawal for patients based on the JSICM criteria as follows[18]:

1. *Generalised symptoms*: unresponsive state; agonised facial expression, pale skin or cyanosis; newly occurred impaired consciousness; agitation with risk to safety; sudden limb weakness or dependence; inability to sustain posture and risk for fall.
2. *Subjective symptoms*: sudden dyspnoea; unbearable fatigue or suffering and desire to withdraw.
3. *Respiration*: respiratory rate <5/min or >40/min; oxygen saturation <88%; increased work of breathing and asynchrony with mechanical ventilation or fighting the ventilator.
4. *Circulation*: heart rate <40/min or >130/min; ECG, newly occurred arrhythmia, sign of cardiac ischaemia; blood pressure, systolic blood pressure >180 mm Hg,

decreased systolic or diastolic blood pressure >20%, mean arterial pressure <65 or>110 mm Hg.
5. *Devices*: risk for unplanned extubation or removal of tube, catheter and drain.
6. *Other conditions*: desire to withdraw from the study; increased drainage of blood and risk for widening a wound.

Randomisation

Patients will be randomised using computer-generated randomisation lists.[19] Randomisation will be stratified by age (<70 years, ≥70 years) and sex (female or male), and the randomisation list will be generated with a block size of 4 before the start of recruitment.[20] The list will be created by an independent person outside the research team. At the allocation, the independent person will check the list and allocate patients either to vibration therapy added to protocolised mobilisation or to protocolised mobilisation alone as the usual standard of care.

Blinding

This study uses a single-blinded trial design because patients can understand the intervention or control by themselves. However, to minimise subject bias, the same vibration device will be used as a footrest for 15 min without vibration by blinded staff. All interventions will be conducted by bedside nurses. The intervention duration will be 15 min and will be conducted when no other staff who are involved in outcome assessments, treatments and usual rehabilitation are present.

Interventions

Vibration therapy

A vibration device (BW-750, BodyGreen) will be used by bedside nurses once daily (figure 2 and online supplemental video file). The device will be used on the feet in the sitting position for 15 min. A low-frequency vibration from 5.6 to 13 Hz with an amplitude of 2 mm in vertical direction can be chosen on the device. This study will use a continuous automatic course of 5.6, 7 and 8 Hz for 30 s each in turn. The number of intervention days will be recorded in compliance with the protocol.

Figure 2 Image of vibration therapy (BW-750, BodyGreen). Consent was obtained for the use of this image.

Protocolised mobilisation

With or without intervention, protocolised mobilisation will be conducted in all patients. Protocolised mobilisation is based on a progressive mobilisation protocol described by Morris *et al*[21] in which the mobilisation level is decided according to patients' consciousness and muscle strength. Passive range of motion is conducted for unconscious patients, whereas in conscious patients, the intensity is gradually elevated to active resistance, sitting on the edge of bed and ambulation. Mobilisation level will be restricted in patients with unstable vital signs.

Primary outcome

The primary outcome is physical function assessment using the Functional Status Score for the ICU (FSS-ICU) at discharge from the ICU, measured by a blinded nurse. The FSS-ICU is a physical function score involving the following five functional tasks: (1) rolling, (2) transferring from resting on spine to sitting, (3) sitting at the edge of bed, (4) transferring from sitting to standing and (5) walking.[22] Each task is scored from 0 to 7, with the maximum score of 35. The research team has conducted a training period for the use of FSS-ICU for 2 months before the start of this study to ensure scoring accuracy.

Secondary outcomes

Medical Research Council score and ICU-AW

After the patients are awake and attentive, nurses evaluate the Medical Research Council (MRC) Score and the incidence of ICU-AW in daily practice. Intact level of consciousness and awareness will be evaluated based on the patient's response to at least three of the following five orders: 'open/close your eyes'; 'look at me'; 'open your mouth and put out your tongue'; 'nod your head' and 'raise your eyebrows'.[23] The MRC Score is the sum of the manual muscle testing in the following six bilaterally tested muscle groups: (1) shoulder abductors, (2) elbow flexors, (3) wrist extensors, (4) hip flexors, (5) knee extensors and (6) ankle dorsiflexors. The ICU-AW is defined as an MRC score of <48 on two separate occasions, and patients with an expected preadmission MRC score of <48 will be excluded in the assessment of the ICU-AW.[24] The research team will use the MRC score and the incidence of ICU-AW at discharge from the ICU for comparison. Blinded nurses will evaluate the MRC score and ICU-AW.

ICU mobility scale

To evaluate the mobilisation level during the ICU stay, the research team will use the ICU Mobility Scale (IMS), which is a measure of mobilisation capabilities from 0 (lying in bed) to 10 (walking independently).[25] In addition to discharge from the ICU, the research team will evaluate the maximum IMS score during the study period because the maximum level of mobility is considered as an important prognostic factor.[26] IMS will be evaluated by blinded nurses as conducted in clinical practice.

Muscle mass

Muscle thickness and cross-sectional area will be evaluated using serial ultrasound measurements at the inclusion and discharge from the ICU.[27] Ultrasound has been identified as a reliable method to measure muscle mass.[28 29] The biceps brachii muscle will be evaluated at two-thirds of the way between the acromion and the antecubital crease, and the thickness is between the superficial fascia of the biceps brachii muscle and the uppermost part of the humerus. The rectus femoris muscle will be evaluated at the midway point between the anterior superior iliac spine and the proximal end of the patella, and the thickness is between the superficial fascia of the rectus femoris muscle and the uppermost part of the femur. A transducer will be placed perpendicular to the long axis of limbs with patients in the supine position under passive limb extension. The muscle mass will be measured three times, and the median value will be used for evaluation. The research team will use the change in muscle mass from the inclusion to discharge from the ICU for comparison. All measurements will be conducted by two examiners. In the authors' previous studies, the intraclass and interclass correlation coefficients were determined to be 0.96–0.99 and 0.98–0.99, respectively.[30]

Delirium

Nurses in the ICU will evaluate delirium using the confusion assessment method for the ICU (CAM-ICU), which includes an acute change or a fluctuation in mental status, altered level of consciousness, disorganised thinking and inattention.[31] CAM-ICU assessment will be performed three times daily as a clinical practice. To evaluate the level of consciousness, the RASS will be used, which ranges from −5 to 4, with lower scores indicating less arousal.[32] The research team will assess the duration of delirium and the state at discharge from the ICU.

ICU-free and ventilator-free days

The *ICU-free days* are defined as the number of days after discharge from the ICU during the 28 days after ICU admission, whereas *ventilator-free days* are defined as the number of days without mechanical ventilation during the 28 days after ICU admission. Patients who die before 28 days without extubation or ICU discharge are counted as no free days, whereas patients who die before 28 days with extubation or ICU discharge are counted as days from the event to the death.

Safety

For evaluating the safety of vibration therapy, vital signs will be monitored from baseline measurements conducted before the start of vibration therapy and 5 or 15 min after the use of therapy. Vital signs will include blood pressure (systolic, diastolic and mean), heart rate and oxygen saturation. Finally, follow-up will be conducted at discharge from the hospital to evaluate the patient's post-study health status and any harmful events. In the authors' facility, no adverse events, as described in the withdrawal criteria, were observed in 30 critically ill patients who were treated with vibration therapy (BW-750, BodyGreen) before the start of this study.

Data collection and management

The research director and the Clinical Research Ethics Committee will supervise the study protocol and data to ensure the accuracy. All data will be presented as requested, and any missing or inconsistent data will be requested or addressed by the research director. Any adverse effects or complications will be immediately reported, and necessary compensation will be provided to any patients who experience harm from trial participation. All records will be retained for 3 years after the completion or termination of the study.

Confidentiality

All datasets will be stored by creating identification codes to anonymise the information of study participants. The coding keys linking identification codes will be stored by the research director. The study participants' information will be protected when publishing the trial results or reporting results at an academic conference. This information will be used only for this research and not for exchange with other facilities.

Data access and dissemination

Study protocol will be available to subjects on request. Study data will also be available for academic, non-commercial research purpose unless the request hinders the protection of personal information or the quality of this study. Individuals involved in this study will have access to the final dataset and will be able to publish the study or report the study at an academic conference.

Patient and public involvement

This study will not involve patients in the development of the research question and outcome measures. They will also not be involved in the design and recruitment. Results will be disseminated to study participants on request.

Sample size

The sample size calculation is based on two studies.[22 33] The FSS-ICU at discharge from the ICU is reported to be 20 (10–30), with a minimal clinically important difference from 2.0 to 5.0. The authors hypothesise that in this study, a 3.0 difference will be observed because vibration therapy is expected to improve standing and ambulating by 2–4. The SD is reported to be 5.9. These data estimate that 171 patients will be required to observe the difference with alpha 0.05 and power of 90%. Assuming a 10% dropout rate due to complete withdrawal or death, a total of 188 patients will be required. Study participants will be randomised either to vibration therapy coupled with protocolised mobilisation (n=94) or to protocolised mobilisation alone (n=94).

Statistical analysis

After data collection, descriptive analyses will be conducted on the obtained data. Continuous data will be presented as mean±SD or median (IQR), whereas categorical data will be presented as number (%). Variables will be compared using the t-test or the Mann-Whitney U-test for comparing the two groups. Efficacy and safety analysis will be conducted in a full analysis set and safety analysis set following the intention-to-treat principle. The full analysis set includes patients who received at least one intervention and had primary outcome assessment. The safety analysis set includes patients who received at least one intervention. In addition, a multivariate and subgroup analysis will be conducted by the duration of intervention, duration of ICU stay before the intervention, mobilisation level (IMS score) and patient's severity (Acute Physiology and Chronic Health Evaluation II score: the score to predict in-hospital mortality in patients admitted to the ICU). If heterogeneity exists, the further analysis will be conducted on the factors. Primary outcome will be compared at discharge from the ICU; secondary outcomes will be compared during the ICU stay or at discharge from the ICU. Missing values at the discharge will be imputed from the last recorded values. Safety analysis will be conducted by comparing the change in vital signs from the start of the therapy session as the baseline to 5 or 15 min after the intervention. Data analyses will be conducted using JMP V.13.1.0 (SAS Institute). All statistical tests will be two-tailed, and $p<0.05$ will be considered as statistically significant.

DISCUSSION

This study describes an intervention protocol of vibration therapy to improve physical function in critically ill patients. Although vibration therapy has been used for decades, its effect remains unclear in the field of critical illness. Several studies have reported the safety of vibration therapy in critically ill patients,[15 34] whereas no studies have been conducted until to examine the efficacy of vibration therapy in critically ill patients.

The randomised controlled trial design is feasible because research has already confirmed that vibration therapy can be used safely in critically ill patients.[34] Vibration therapy is typically used for days or weeks; however, some patients in the ICU stay for a short time (<1 week). In Japan, 38.9% of patients are admitted to the ICU only for monitoring, and the median length of ICU stay is 2.5 (1.4–4.8) days in critically ill patients.[35] Therefore, the selection of patients is important, and this study will enrol those patients who are expected to require further ICU stay after the intervention. Vibration therapy will be used for 15 min/day, which has been confirmed to be safe in critically ill patients.[15] In previous studies, vibration therapy for 6–18 min/day was found to be beneficial in patients with cystic fibrosis or stroke.[36 37] In those studies, vibration therapy was used for weeks to months; however, in this study, the intervention duration will depend on the time from the first use of vibration therapy in the ICU to discharge from the ICU. Therefore, a multivariate and subgroup analysis by the intervention duration is necessary because it is unclear how the short-term use of vibration therapy affects physical function. Moreover, the duration of ICU stay before the intervention needs further analysis because muscle atrophy and weakness should be more critical at the time of later intervention.

Among the different vibration devices, the frequency of vibration varies from 2 to 90 Hz. Although the vibration frequency of 2 Hz is too low to have a treatment effect,[38] higher vibration frequencies have some effect. This study will use a relatively low-frequency vibration device (5.6–8 Hz). These frequencies of vibration are useful to improve physical function, and a vibration of 5–14 Hz has been demonstrated to significantly improve physical function, including gait speed and handgrip strength.[39] In another study, a low frequency ranging from 2 to 20 Hz was found to improve muscle strength for the knee extensor.[40] A recent study that used the same vibration device that will be used in this study, the BW-750, BodyGreen, reported that this device was useful in improving the muscle strength of knee extensor in patients with post-total knee arthroplasty.[41] Furthermore, low-frequency vibrations of 12–15 Hz were found to have more beneficial effects on bone mass than vibrations of 30–90 Hz or even than walking.[42 43]

In addition to the vibration frequency, the posture is an important component for successful vibration therapy. In our study, vibration therapy will be used in patients in the sitting position, whereas the majority of vibration therapy sessions are conducted in the standing position.[41 44] We will use vibration therapy in the sitting position because standing is conducted in only 1%–2% of critically ill patients.[8 45] Vibration therapy in the sitting position is also beneficial because Faes *et al* have reported that foot-transmitted vibration in the sitting position can improve balance and flexibility.[46] This foot-transmitted vibration in the sitting position can be equivalent to whole-body vibration, not partial-body vibration, because the vibration is transmitted to the whole body.[46] On the other hand, we will not use vibration therapy in the flat position because it may not have sufficient load in the flat supine position.[34] In addition, from the authors' experience, vibration therapy in the flat position may cause additional stress for critically ill patients when they are confined to the bed.

In this study, we set FSS-ICU as the primary outcome of this research because it is a reliable functional score in the ICU.[33] FSS-ICU at discharge from the ICU can predict discharge home at an AUC of 0.88 (0.77–0.84), which is preferable than the IMS score of 0.73 (0.68–0.77).[47] In the study, an FSS-ICU ≥19 had a sensitivity of 82.9% and a specificity of 79.7% to predict discharge home.[47] We consider physical function as an important functional outcome because functions require not only muscle strength but also postural control, endurance, cognition

and response to the change.[48] Therefore, we will use FSS-ICU as a primary outcome rather than MRC Score.

The research team will monitor muscle mass because it is difficult to assess physical function in some critically ill patients.[49] Muscle atrophy is a critical problem in the ICU, and in 1 week, the decreased muscle mass reaches the degree of 13.2%–16.9% and 18.8%–20.7% in the upper and lower limbs, respectively.[30] Furthermore, muscle atrophy occurs in respiratory muscles.[50] Vibration therapy has reportedly contributed to preventing limb muscle atrophy. In one study, vibration therapy contributed to preventing the loss of quadriceps femoris muscle mass in healthy volunteers (−3.3% vs −14.4% in 56 days).[51] Vibration not only serves as resistance training but also provides the stimulation that can promote the proliferation of myoblast cells and downregulate the expression of atrophy genes.[52] We will monitor muscle mass using ultrasound because biomarker level is increased in surgical patients who will be included in this study.[53]

Delirium has been observed in 30% of critically ill patients,[54] and the duration is associated with long-term cognitive dysfunction.[55] Delirium is another significant cause of PICS. The authors believe that vibration therapy will contribute to improving delirium based on three reasons. First, enhanced rehabilitation using vibration therapy will contribute to decreasing delirium[6] because early mobilisation has been reported to reduce the number of days of delirium (2 vs 4, p=0.03).[56] Second, vibration therapy improves circulation. Low cerebral perfusion is a risk factor for delirium, and a 10 mm Hg decrease in cerebral perfusion has an OR of 2.08 (95% CI, 1.02–4.24) in predicting delirium.[57] Vibration can improve circulation to vital organs, including the brain.[58] This effect has also been confirmed through a post-cardiac arrest model using pigs.[59] The mechanism is considered to be increased nitric oxide or decreased endothelial damage.[60 61] Third, vibration therapy affects the hormone signals produced from the body.[62] The growth hormone, whose levels are increased by vibration, has neuroprotective properties that may improve delirium.[63]

There are several limitations in this study. First, this study will provide the results of vibration therapy added to protocolised mobilisation, not the results of vibration therapy alone. The effects may be limited in patients who cannot perform active mobilisation, because a recent study demonstrated that electrical muscle stimulation and in-bed leg cycling did not improve physical function in patients who had active mobilisation.[64] Electrical muscle stimulation was effective in patients with limited mobilisation.[65] Therefore, a multivariate and subgroup analysis is required to determine the effect in patients for whom active mobilisation is limited. Second, the intervention period is different among subjects. The intervention may be conducted for a short-time period due to ICU discharge, intolerance and death. An organised intervention period is desirable but not feasible in the ICU. Therefore, we will conduct a multivariate and subgroup analysis in the intervention period. Third, due to the single-centre design, heterogeneity may exist, thereby requiring further analysis on the factors. Fourth, double blinding is not feasible because patients can understand the intervention or control. Therefore, some bias may remain, although the outcome assessment is blinded.

ETHICS AND DISSEMINATION

This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital (approval number 3763). At the time of enrolment, written informed consent will be obtained from patients or their authorised surrogate decision-makers. The study participants' information will be protected at all times, and all data will be stored securely. Results will be disseminated through publication in a peer-reviewed journal and presented at conferences.

Trial status

This trial is not recruiting patients at the time of manuscript submission.

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