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PERSPECTIVE

Guidelines for Early Mobilisation of Intubated Patients in Intensive Care Unit: Clinical Pathology Evidence-Base Perspective

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Abstract
Intensive care unit (ICU) patients can be immobilised over long periods due to their conditions, and the subsequent management inclusive of mechanical ventilation, which is also associated with complications. Hence, early mobilization of intubated patients (EMIP) may be beneficial but there are various barriers including the lack of consensus guidelines. Based on a brief scoping literature review, this article notes of perhaps one consensus guidelines developed from a systematic review in 2014 followed by a meeting of experts from ICU but there are other guidelines, recommendations, and strategies. However, there still exists the challenge of consensus guidelines for early mobilization. Barriers and/or facilitators, evaluation of optimal intervention dosage, good communication, and use of necessary assistive equipment have also been identified. Some resource limited countries lack physiotherapists and equipment, and these services are therefore provided mostly by nurses and junior doctors, which calls for tailored guidelines. Prominent note in the guidelines is oximetry but not blood gas measurement and another note are the limitations caused by vasoactive agents. Perhaps, the cost and invasive nature of the blood gas analyses are concerns and this is significant for resource limited countries. However, this test and alternatives need considerations in the guidelines. There is agreement on safe early mobilisation of intubated patients (EMIP), but this requires developing to tailor for resource limited countries. The vasoactive agents affect blood gases, hence evidence-base blood gases and acid–base analyses are necessary to integrate in monitoring intubated patients in ICU. Given the four criteria (cardiovascular, neurological, respiratory, and 'others') and challenges in the existing guidelines, some laboratory tests are recommended as additional items to the 'others' criterion to improve on potential points of imprecision and risk of bias.

Keywords Blood gas analyses · Mechanical ventilation · Intubation · Mobilisation · ICU

1 Introduction

Intensive care unit (ICU) patients have long periods of immobilisation due to their critical conditions, and the associated management regimes such as mechanical ventilation [1]. Globally, about 13–20 million patients are managed in ICUs annually. In patients who have had mechanical ventilation for more than 48 h, wasting of skeletal muscles is seen and various reasons are cited including the pathophysiology of critical disease. Early mobilisation of intubated patients (EMIP) is an established clinical management protocol. However, studies have reported seemingly conflicting perspectives [2, 3], leading to opinion that early active mobilisation of intubated ICU patients may do more harm than good [4].

Patients on prolonged invasive mechanical ventilation, are prone to immediate high risk of muscle atrophy, and severe weakness, among others [5, 6], and further the process is an invasive airways procedure involving cardiorespiratory physiology. Hence, acute management of critically ill patients in the ED is commonly based on blood gas analysis [7, 8]. Therefore, it is important to consider guidelines and

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recommendations taking into account accessibility of the test in communities that have limited resources.

2 Focus of Perspective

Three questions constituted the basis of this paper—viz: What are the guidelines for early mobilisation of intubated patients in ICU? What are the challenges in early mobilisation of intubated patients in ICU? How is evidence-base laboratory medicine such as blood gas analysis employed in determining early mobilisation of intubated patients in ICU?

Four points-of-interest highlighted in the discussion include advantages of EMIP, planning and method of early mobilisation, and considerations of administration of vasoactive agents with evidence-base laboratory.

3 Literature Search

The brief literature search was discretionally limited to PubMed platform and the whole term "*early mobilisation of intubated patients in ICU*". Themes of interest used for selection of literatures for critical review were based on clinical laboratory monitoring perspective hence, included 'guidelines', 'challenges', and 'blood gas analyses.

The main search yielded 52 articles including 16 free full texts, amongst which is the 36th International Symposium on Intensive Care and Emergency Medicine [9]. Among the 16 full texts, only one (6.25%) is expert consensus recommendations i.e., guidelines [10], while another two papers (12.50%) discussed challenges [1, 11]. Within the symposium abstracts that comprised 461 items, four items selected that touched on laboratory perspectives.

4 Discussion

4.1 What are the Guidelines for Early Mobilisation of Intubated Patients in ICU?

The brief literature search highlights that there exists probably one consensus guidelines' recommendation that was developed from systematic review in 2014 and a meeting of multidiscipline experts from ICU. According to the authors, consensus was reached on the criteria for safe mobilization, but not on the levels of vasoactive agents [10].

In a systematic review update of guidelines for clinical practice [12], seven points were itemized that could be termed as recommended principles and guidelines. The principle itemized is mainly that EMIP can be safe and capable of reducing the cost of patient's healthcare. The guidelines, which were six, recommend that the EMIP program be outlined especially in terms of outcome evaluation. Other recommendations include requirements for standard operational protocol, skills set of the healthcare clinician, safety checklist, multidisciplinary teamwork, and engagement of the patient and family caregivers. It was recommended, as part of the conclusion, that significant deviations existed in the quality of clinical practice approaches, and that future research addresses gaps regarding patient selection [12]. Further, one of the authors of the consensus guidelines in 2014 and update of 2020 lead a team of four colleagues to suggest another list of recommendations [13], and two points are pertinent to note. First, it was identified that up to eight international guidelines were developed. Second, the recommendations increased to 10 strategies. In addition to the previously listed six requirements, the add-on four recommendations included identifying barriers and/or facilitators, evaluating optimal intervention dosage, good communication between teams, and use of necessary assistive equipment. This is echoed in the recommendation of future trends [3].

There have studies in the Americas, for instance, a Brazilian guideline that seems to have developed from systematic literature review and was based on six pertinent questions including contraindications and prognostic indicators such as oxygen saturation monitoring. This study among others, noted that early mobilization is associated with superior functional outcomes and need to be carried out whenever required, and is safe, hence should be the aim of the multidisciplinary team [14]. Another report of a cross-sectional study involving seventeen Latin American countries highlight EMIP to be an established clinical practice, though standard protocol existed for only 36.1% of cases [15].

4.2 What are the Challenges on Early Mobilisation of Intubated Patients in ICU?

From the two papers that highlighted the challenges, each suggested a theme.

Data from India was based on quality improvement initiative clinical audit to identify challenges and advocated as with other recommendations, a multidisciplinary approach for significant improvements in early mobilization [1]. The second paper is on children and premised on the known challenge of oversedation and/or undersedation. The authors indicate that literature favours protocol of goal setting based on sedation scoring; but that ages and pharmacological differences in drugs make it difficult to standardized practice [11].

Further, another paper enunciated the challenges to implementing the existing consensus guidelines [16]. The enunciation is based on observational study of 280 consultations in 100 patients and the report highlighted two barriers. Firstly, among those identified with low risk, 40% could not

be mobilized and time-constraint is the barrier. Secondly, in those with high risk of adverse event, sedative is the barrier in 82% of the patients.

In the clinical trial report of Hodgson et al. [5] on "early active mobilization during mechanical ventilation in the ICU", results show no difference between intervention group compared to usual care group. The activities of daily living, cognitive function, disability, psychological function, and quality of life showed no significant difference between both groups [5]. In the clinical trial, use of vasoactive agents and sedation scores were similar in both groups. However, some pertinent challenges are highlighted in the study limitations, some of which are outlined as follows:

- "Mobilization levels that were achieved in the usual-care group were … similar to the control group of a previous clinical trial showing benefits from early mobilization." However, a brief critical review shows (Table 1) that the referred previous study had relatively more cardiorespiratory diagnosis in control group relative to intervention group [17]. Thus, it is possible that benefits observed in the previous study could have been swayed by the relatively less cardiorespiratory prevalence in the intervention group.

"Our protocol stipulated that whenever it was feasible to do so, patients in the usual-care group should receive treatment from physiotherapy staff members." It is pertinent to emphasize the "whenever it was feasible to do so" in this recommendation in protocol. Indeed, many resources limited communities lack professional physiotherapists and necessary assistive equipment. In some cases, such professions are not available, hence these necessary services are provided mostly by nurses and junior doctors. The implication is that guidelines be tailored to cater for such situations.

Table 1 Cardiorespiratory characteristics between groups in the two studies compared

	Diagnosis	Intervention	Usual care
New study based on consensus recommendation	Sepsis	246	245
	Trauma	15	14
	COVID-19	7	10
	Total	268	269
Older study prior to consensus recommendation	Acute lung injury	27	31
	COPD	4	6
	Asthma	5	4
	Sepsis	7	9
	Haemorrhage	1	2
	Total	44	52

4.3 How is Evidence-Base such as Blood Gas Analysis Employed?

Prominent point of note in the guidelines is indicated in the use of oximetry but not blood gases and acid base measurements. Given that it is developed by Australian clinicians who have access to blood gas analysis, it behoves that practitioners in resource-limited settings probably lack the motivation to consider such test. However, research to elucidate gaps in patient selection had been suggested [12], hence a discretional question about evidence-base use of blood gases and acid base analyses.

Among the four abstracts selected from the international symposium [9], two employed blood gas analysis. The first (abstract #181) reported a case of intubation informed by arterial blood gas, which showed both metabolic and respiratory acidosis. The second (abstract #234) reported on cases of haematological malignancy and the need for non-invasive ventilation (NIV) monitored with blood tests including blood gas analysis. Interestingly, the report highlights that cases of NIV failure have abnormal $PaCO_2$ and FiO_2 [9]. That is, blood gas analysis can be combined with pulse oximetry to make informed decision.

Perhaps, the cost and invasive nature of the blood gas analysis test are probable concerns that must be acknowledged [18]. This is particularly significant for resource limited settings and where healthcare costs are paid off-pocket. However, this test and potential alternatives would need to be considered for integration in future updates of the guidelines.

4.4 Four Points-of-Interest in Brief

1. **Advantages of EMIP**: Studies report that early mobilization of patients may have positive effects but there are barriers, further early mobilization may not be sufficient to reduce ICU-acquired weakness and may also carry risks, which sustains some controversies necessitating further recommendations [2, 3]. EMIP in ICU is therefore a concern for the patients, clinical team, and public health officers [5]. There are studies that have reported that early active mobilisation of intubated ICU patients may do more harm than good [4]. Of note, some authors of the consensus guidelines have asked whether "to mobilize or not to mobilize" is the appropriate question and some have highlighted difficulties in determining evidence for decision on early mobilization [6].
2. **Planning and method of early mobilisation**: EMIP involves planning, implementation, and evaluation phases. Thus, in this agenda-perspective, an articulation of the SMART components becomes imperative in the plan—re: what is the **specific** objective for the early mobilization? How would the objective and subsequent

success of the EMIP be **measured**? While **achievability** checks would require compliance to methodological guidelines, the **reality** check calls for evaluations of the *pros and cons* of the selected method as well as risks and side-effects of the EMIP. Perhaps, time frame may be a no brainer, but ideally planning is required at the start of intubation.

On the methods, it is a given that early mobilization involves optional sets of activities of daily living. This opinion on SMART plan is in line with indicated guidelines, that is, EMIP program should include outline of safety checklist (planning phase), standard operational protocol (implementation phase), and outcome evaluation (evaluation phase), among others [12].

3. **Consideration of vasoactive agents**: The literatures have indicated agreement on the criteria for safe mobilization; but appear to indicate no consensus on the levels of vasoactive agents [10]. At this juncture, it is pertinent to emphasize that while expert consensus guidelines were based on risk classification instead of sedation scoring, critical thinking would reveal some agreement between these authors' opinion and the consensus guidelines. That is, the challenge of developing consensus guidelines for early mobilization exists only when analgesic and vasoactive agents are involved.

   Therefore, it is expedient to review the planning and evaluation phases of EMIP programs, where vasoactive agents have been involved. Perhaps, the review of safety checklists alongside sedation scoring may advance our knowledge and practice. Further review of how outcomes are being evaluated may lead to some consensus.
4. **Vasoactive agent versus evidence-base monitoring:** The effects of vasoactive agents on blood gas changes have been reported [19, 20]. Blood gases and acid–base analyses are integral to monitoring intubated patients in ICU, therefore, these analyses perhaps need to be considered, for example, to determine need and levels of administered vasoactive agents. For instance, it has been known that intubation is unnecessary where non-invasive ventilation (NIV) is successful, and that NIV failures are associated with abnormal blood gases and use of vasoactive agents [9]. Perhaps, it is pertinent to highlight that even the antibiotic isoniazid has been reported to cause anion gap enroute metabolic acidosis. These highlight the need to go beyond sedation scores and consider integration of laboratory evidence-base protocol in EMIP where vasoactive agents are involved.

5 Development/Recommendations

5.1 Premises of Recommendation

This development or recommendation is based on two premises. First is the already existing expert consensus guidelines [10], as well as challenges [1, 11]. However, the guidelines have yet to integrate laboratory evidence-base. Second is that intubation is unnecessary where NIV is successful, and NIV failure is associated with abnormal ABG and/or vasoactive agents [9]. Hence the need to consider laboratory evidence-base protocol in EMIP regimen that involves vasoactive agents.

Third is the GRADE approach for assessments of certainty, which considers five areas including imprecision, inconsistency, indirectness, publication bias and risk of bias [21]. On this occasion, imprecision in the current guidelines is the lack of laboratory evidence-base. For instance, monitoring of respiratory insufficiency is imprecise and need to be supported with ABG [22], just as assessment of the effects of vasoactive agents [19, 20] (Table 2).

5.2 Objective of Recommendation

To integrate laboratory monitoring as evidence-base in the existing EMIP guidelines. It is important to emphasize that the objective these additional items is NOT to develop a brand-new guideline, but to add some ascertainment steps to improve potential points of imprecision and risk of bias in the existing one.

5.3 Justification of Recommendation

ABG monitoring has been used in clinical review of ventilation settings and intervention intubation, but inconsistently [23]. Further, ABG and acid–base balance monitoring are associated with NIV and use of vasoactive agents [9, 19, 20].

5.4 Significance of Recommendation:

Considering that pharmacological differences in drugs has been a challenge to standardized practice [11], and the association of with abnormal blood gases with vasoactive agents [9]; the additional step of laboratory monitoring in the guidelines could assess the certainty of effect of EMIP regimen. As per emphasis on objective, the main significance of this recommendation is, based on the GRADE

Table 2 Current criteria and additional items

	Safety criteria	In-bed exercises	Out-of-bed exercises
Existing guideline [10]	Respiratory safety* Cardiovascular safety** Neurological safety*** Others†	as recommended in existing guideline	
Additional items to the ''Others' criterion'	Pulse oximetry: for respiratory insufficiency‡	▲	⬢
	Transcutaneous blood gas monitoring‡‡	▲	▲
	ABG and electrolytes monitoring	●	▲
	Anaemia and thrombocytopaenia†‡	▲	⬢

Keys:

*Including adjunct therapy, intubation status, ventilatory parameters

**Including blood pressure, arrhythmias, and presence of devices

***Including consciousness, delirium, and intracranial pressure

†The 'Others criterion' includes medical consideration, that further incorporate suspicion of bleeding and pharmacological cooling management (re: sedatives). Further considerations include femoral and central venous catheters

‡Imprecise if peripheral perfusion is decreased. Hence risk of interpretation bias and need to be supported with ABG [22]

‡‡Inferior to ABG. Hence could be confirmed with ABG [22]

†‡Laboratory measure to ascertain consideration of bleeding in existing guideline

concept [24], for improvement on the point of imprecision in the existing guideline. Further, this recommendation is strong where vasoactive agent has been used.

6 Conclusion and Recommendation

There is agreement on the need for safe EMIP. However, there is also room to improve on the existing guidelines, even if this requires developing guidelines that are tailored to resources limited settings. Another point of note is the adoption of evidence-base laboratory test using blood gas and acid base analyses, which seem used in some studies but not contained in current recommended guidelines.

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