Australian Critical Care 32 (2019) 139–146

Contents lists available at ScienceDirect

Australian Critical Care

journal homepage: www.elsevier.com/locate/aucc

Research paper

Mobilisation is feasible in intensive care patients receiving vasoactive therapy: An observational study

Anneke Rebel, BPhysiotherapy (Hons) [a]
Vince Marzano, BPhysiotherapy (Hons) [b]
Margot Green, BApp Sc (Physiotherapy) [b]
Karlee Johnston, MClin Pharmacy [b]
Jiali Wang, MSc [c]
Teresa Neeman, PhD [c]
Imogen Mitchell, PhD [b, d]
Bernie Bissett, PhD [a, b, *]

[a] Discipline of Physiotherapy, University of Canberra, Australia
[b] Canberra Hospital, ACT Health, Canberra, Australia
[c] Statistical Consulting Unit, Australian National University, Canberra, Australia
[d] Medical School, Australian National University, Canberra, Australia

ARTICLE INFORMATION

Article history:
Received 1 November 2017
Received in revised form
13 March 2018
Accepted 13 March 2018

Keywords:
Physiotherapy (techniques)
Critical care
Intensive care
Mobility

ABSTRACT

Background: Mobilisation of intensive care unit (ICU) patients reduces ICU-acquired weakness and is associated with better functional outcomes. However, the prevalence of mobilisation of ICU patients remains low. A known barrier to mobilisation is haemodynamic instability, frequently with patients requiring vasoactive therapy. There is a lack of published data to guide clinicians about the safety and feasibility of mobilising patients receiving vasoactive therapy.

Objectives: To describe our mobilisation practice in ICU patients receiving vasoactive therapy and identify factors associated with mobilisation and adverse events.

Methods: Retrospective cohort study of patients undergoing vasoactive therapy in a 31-bed tertiary ICU (October–December, 2016). Details of vasoactive drug dosage, mobilisation, and adverse events were extracted from databases, including mobilisation intensity (ICU Mobility Scale [IMS]). Two generalised linear mixed models were used: first, to describe factors associated with mobilisation and second, to describe factors associated with adverse events during mobilisation, adjusting for age, gender, and acute physiology and chronic health evaluation II score as co-variates.

Results: In 119 patients undergoing vasoactive therapy on 371 cumulative vasoactive days, 195 mobilisation episodes occurred (37.5% of vasoactive days). Low (76.8%) and moderate (13.7%) dose vasoactive therapies were associated with a higher probability of mobilisation relative to high (9.4%) dose therapy (odds ratio = 5.50, 95% confidence interval = 2.23–13.59 and odds ratio = 2.50, 95% confidence interval = 0.95–6.59, respectively). For patients who mobilised on vasoactive therapy (n = 72), maximum mobilisation intensity was low (IMS = 1–2) in 31%, moderate (IMS = 3–5) in 51%, and high (IMS = 6–10) in 18% of vasoactive days. While no serious adverse events occurred, there were 14 occurrences of reversible hypotension requiring transient escalation of vasoactive therapy (7.3%), associated with lower mean arterial pressure (p = 0.001).

* Corresponding author at: Discipline of Physiotherapy, University of Canberra, Australia. Tel.: 61 2 6201 2566.
E-mail address: Bernie.Bissett@canberra.edu.au (B. Bissett).

https://doi.org/10.1016/j.aucc.2018.03.004

Conclusion: In our ICU, patients mobilised on approximately one-third of vasoactive days. Clinicians should anticipate a higher risk of hypotension during mobilisation in patients receiving vasoactive therapy, which may require transient escalation of vasoactive therapy.

1. Introduction

There is mounting evidence that mobilisation commenced during the intensive care unit (ICU) admission can improve recovery trajectories for survivors.[1] Early mobilisation reduces ICU-acquired weakness[2] and improves functional outcomes at ICU discharge,[3,4] which may translate into reduced ICU and hospital length of stay[5] as well as longer term positive effects on physical function,[6] lower rates of hospital readmission,[7] and reduced 12-month mortality.[8] Surprisingly, very few ICU patients are mobilised in Australia and New Zealand[2,9] (e.g. 16% in a study of patients across 12 ICUs[2]). Low incidences of mobilisation have been similarly reported in United States[10] Scottish,[11] and German[12] observational and point prevalence studies. Clinician-reported barriers to mobilisation in ICU frequently include haemodynamic instability and vasoactive drug use.[2,9,12]

Many patients require vasoactive therapy during their ICU admission.[13] In a binational multicentre cohort study of Australian and New Zealand ICUs,[2] 66% of patients mechanically ventilated for more than 48 h underwent vasoactive therapy at one or more points during their admission.[2] In this cohort, vasoactive therapy was the third most commonly reported barrier in patients who did not receive early mobilisation.

Several studies of mobilisation in ICU patients describe the need for ongoing vasoactive therapy as an indication of insufficient cardiovascular reserve to perform mobilisation activities and either defer mobilisation in these patients[14–17] or altogether exclude them from their sample.[18] The 2014 expert consensus recommendations on safety criteria for mobilisation in ICU, involving 23 multidisciplinary ICU experts, were unable to reach consensus on the definition of haemodynamic instability and criteria for acceptable levels of vasoactive agents. Other guidelines offer only arbitrary specifications of acceptable vasoactive drug dosages (e.g. noradrenaline dose of 0.1 μg/kg/min).[19] Thus there is little data to guide ICU clinicians about the safety of mobilising patients who are dependent on vasoactive therapy.[20]

The purpose of this study was to explore and describe how patients receiving vasoactive therapy are mobilised in our Australian ICU and provide clearer insights into the factors which are associated with mobilisation, or adverse events, in this potentially less stable cohort of patients.

2. Methods

2.1. Research design

A retrospective cohort study was performed, capturing all consecutively admitted critically ill patients receiving vasoactive therapy from 1 October 2016 to 31 December 2016. Ethical approval for this project was obtained through Australian Capital Territory Health and University of Canberra Human Research Ethics Committees (ETHLR.16.145), and informed consent was waived. The study was registered on the Australian Clinical Trials Registry on 6/12/2016 (Trial ID: 12616001678482).

All information required for this study was routinely collected, recorded, and stored in the ICU electronic clinical information system as part of standard practice by ICU physiotherapists, doctors, and nurses. Data extracted included automatically imported data from real-time monitoring of vital signs (e.g. mean arterial pressure, oxygen saturation, and respiratory rate) and manually entered data documented by clinicians at the time of treatment (e.g. distance mobilised, reasons to cease mobilisation, and patient response to treatment).

2.2. Study setting

The study was conducted in an Australian 31-bed medical, surgical, and trauma ICU. This ICU has a well-established mobilisation culture, attaining rates of mobilisation higher than national averages (i.e. mobilisation occurs on 54% of patient days in our unit).[21]

In this ICU, all patients are evaluated daily by the multidisciplinary team for their suitability to participate in mobilisation. Mobilisation is defined as any activity that facilitates active in-bed and active or passive out-of-bed movement.[1] While the aim is to achieve the highest level of active mobilisation possible, mobilisation can be facilitated passively if patients are unable to actively participate (e.g. tilt-tabling or hoist transfer). In our unit, vasoactive therapy is not considered a contraindication to early mobilisation. A more detailed practical description of our mobilisation practices can be found elsewhere.[22]

2.3. Participants

Eligible patients participants were adult ICU patients receiving vasoactive therapy at one or more points during their admission in the study period. Vasoactive agents included noradrenaline, dobutamine, vasopressin, adrenaline, levosimendan, milrinone, and metaraminol administered alone or in combination via intravenous infusion (see Table 1). Eligible participants were identified by the senior ICU physiotherapist through screening of routine statistical data, and these were confirmed with cross-reference to the electronic database.

2.4. Outcomes

The outcomes were

1) the frequency and intensity of mobilisation in patients receiving vasoactive therapy and
2) the occurrence of adverse events during mobilisation.

The frequency of mobilisation was described as the number of mobilisation episodes that coincided with administration of vasoactive therapy, as documented in electronic database by the treating physiotherapist or nurse. For each episode of mobilisation, the profession of the staff member leading the mobilisation (i.e. nurse or physiotherapist) was also captured.

The intensity of mobilisation achieved during each episode, as described by the treating clinician in electronic health records, was quantified using the ICU Mobility Scale (IMS). The IMS has established strong inter-rater reliability ($r = 0.83$),[30] moderate validity

(r = 0.64),[31] and high responsiveness (d = 0.8)[31] as a measure of mobility in critically ill patients.

The incidence of adverse events was determined from physiotherapy and nursing documentation in the electronic health records. Adverse events were defined a priori as a fall to the ground, cardiac arrest, unplanned extubation, new onset of cardiac dysrhythmias, removal of invasive lines and tubes, loss of consciousness, hypotension necessitating escalation of medical therapy (as determined by the treating clinicians, rather than an absolute threshold), and death.[2,4,32] These events were deemed a serious adverse event if they resulted in death or persistent or significant incapacity or prolongation of hospitalisation.[33] Data about subsequent management for adverse events, including whether additional medical intervention was required to regain stability, were also extracted.

Where mobilisation coincided with administration of vasoactive infusions, data including vasoactive drug dosage, cumulative day of vasoactive therapy, heart rate, respiratory rate, mode of ventilation, presence of continuous renal replacement therapy, and mean arterial pressure were extracted. Vasoactive drug dosage at the time of mobilisation was derived from automated drug administration records of vasoactive infusions. Vital signs at the time of mobilisation were captured as observed and documented by physiotherapists or nurses during the episode of mobilisation. However, if this information had been omitted in documentation, vital signs were inferred from automated hourly imported values that were captured from continuous monitoring using the most recent value available before the mobilisation episode.

For patients who did not receive mobilisation while undergoing vasoactive therapy, reasons for withholding mobilisation were also extracted from documentation. Vasoactive drug dosage for this subset was captured at the time of documentation of clinical reasoning for withholding mobilisation.

2.5. Data analysis

Descriptive analyses were used to describe patient demographics, frequency of mobilisation, intensity of mobilisation, vasoactive drug dosages, and incidence of adverse events/early cessation of treatment. Intensity of mobilisation was stratified into low, moderate, and high intensity. Bed exercises or passive transfers (IMS 1–2) were classed as low intensity, actively moving in- or out of bed (IMS 3–5) were classed as moderate intensity, while marching on the spot or ambulating away from the bedspace were classed as higher intensity (IMS 6–10). Heterogeneous vasoactive agents and dosages were also stratified into high, moderate, and low categories (Table 1).

Two generalised linear mixed models were used to determine (1) whether any factors were associated with an increased likelihood of mobilisation, adjusting for age, gender, and disease severity (acute physiology and chronic health evaluation II score [APACHE II])[34] as co-variates and (2) to identify any factors significantly associated with an increased risk of adverse events. The association between explanatory variables and binary outcomes were expressed as odds ratios (ORs) and 95% confidence intervals (CIs), and $p < 0.05$ was considered statistically significant. Day of vasoactive therapy was categorised into 1 (day 1), 2 (day 2), 3 (day 3), 4 (day 4), 5 (day 5–9), and 6 (day 10+). Owing to the small number of adverse events in our sample, vasoactive drug dosage during mobilisation was further categorised into “lower dose” (low dose) and “higher dose” (moderate and high dose) for the adverse events model.

Statistical analyses were performed using SPSS (version 23, IBM Crop, Armonk, New York, USA) and R 3.3.1 (https://www.r-project.org/).

3. Results

3.1. Demographics

In total, 119 patients underwent vasoactive therapy during their admissions to ICU over a 3-month period (Table 2). Of these, 70 were female (59%), and the mean age was 68 years. The most common reasons for being admitted to ICU were primary cardiovascular/vascular diagnoses (30%), sepsis (25%), and respiratory failure (18%). The mean (standard deviation) APACHE II score was 21.4 (7.7), indicating moderate disease severity on admission to ICU.[34]

3.2. Vasoactive therapy and mobilisation

Patients received vasoactive therapy on a median of 3 days (IQR 2–5 days) (Table 3). Vasoactive drug dosages were low on 77% (n = 285), medium on 14% (n = 51), and high on 9% (n = 35) of vasoactive days. Noradrenaline was the most frequently administered vasoactive agent (74.4% of vasoactive days), with a mean dose of 6.7 μg/min.

In 119 patients undergoing vasoactive therapy during their ICU admission, translating to 371 vasoactive patient-days, 195 episodes of mobilisation occurred. That is, 72 of the 119 patients (61%) mobilised on at least one vasoactive day. In total, patients mobilised on 37.5% of all vasoactive days (139/371). Maximum level of mobilisation achieved per day was low (IMS = 1–2) on 31% (n = 43), moderate (IMS = 3–5) on 51% (n = 71), and high (IMS = 6–10) on 18% (n = 25) of vasoactive days (see Table 4). Patients receiving low dose vasoactive therapy were mobilised on 44% of vasoactive days. Patients receiving moderate dose therapy were mobilised on 22% of days, and patients receiving high dose therapy were mobilised only on 6% of days. Of those mobilised, mechanical ventilation and renal replacement therapy were present on 28% and 10% of vasoactive days, respectively.

For patients who were not mobilised while undergoing vasoactive therapy (62.5% of days), the most common reason provided for withholding mobilisation was clinician-perceived physiological

Table 1
Stratification of vasoactive agents and dosages.

Class	Agent	Low	Moderate	High
Vasopressor	Noradrenaline[23,24]	<15 μg/min	15–30 μg/min	>30 μg/min
	Metaraminol[25]	0.5 μg/kg/min	1–5 μg/kg/min	>5 μg/kg/min
	Vasopressin[23]	<0.03 units/min	0.03 units/min	>0.03 units/min
	Adrenaline[24,26]	<15 μg/min	15–30 μg/min	>30 μg/min
Inotrope	Dobutamine[27,28]	<5 μg/kg/min	5–10 μg/kg/min	>10 μg/kg/min
	Milrinone[25]	0.5 μg/kg/min	2.5 μg/kg/min	5 μg/kg/min
	Adrenaline[24,26]	<15 μg/min	15–30 μg/min	>0.5 μg/kg/min
	Levosimendan[29]	0.05 μg/kg/min	0.1 μg/kg/min	0.2 μg/kg/min

Table 2
Demographic characteristics of patients receiving vasoactive therapy (n = 119).

Age [years], mean (SD)	68 (11)
Female, n (%)	70 (59)
Weight [kg], mean (SD)	80 (21)
APACHE II score, mean (SD)	21.4 (7.7)
ICU mortality, n (%)	10 (8.2)
ICU LOS (days), median [IQR]	7 [4, 15]
Total admissions, n	122
Vasoactive days per admission, median [IQR]	3 [1, 5]
Primary admission diagnosis, n (%)	
Cardiovascular/vascular	37 (30)
Sepsis	30 (25)
Respiratory	22 (18)
Gastrointestinal	7 (6)
Renal	5 (4)
Other surgical	13 (10)
Other medical	8 (7)

APACHE II = acute physiology and chronic health evaluation II score; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; SD = standard deviation.

Table 3
Characteristics of vasoactive drug support.

Total vasoactive days, n	371		
Vasoactive days per admission, median [IQR]	3 [1, 5]		
	All (n = 371)	Mobilised (n = 139)	Not mobilised (n = 232)
Vasoactive dosage per total vasoactive days, n (%)			
Low	285 (77)	126 (44)	159 (56)
Medium	51 (14)	11 (22)	40 (78)
High	35 (9)	2 (6)	33 (94)
Vasoactive agent per total vasoactive days, n (%)			
Noradrenaline	276 (74.4)	117 (42)	159 (58)
Dobutamine	4 (1.1)	2 (50)	2 (50)
Metaraminol	45 (12.1)	16 (36)	29 (64)
Other	1 (0.3)	0 (0)	1 (100)
Combination of two agents	30 (8.1)	3 (10)	27 (90)
Combination of three agents	15 (4.0)	1 (67)	14 (33)

IQR = interquartile range.

Table 4
Mobilisation characteristics of sample.

Total vasoactive mobilisation days, n (% of total vasoactive days)	139 (37.5)
Vasoactive mobilisation days per ICU admission, median [IQR]	1 [0,2]
Total vasoactive mobilisation episodes, n	195
Maximum intensity of mobilisation per vasoactive day, n (%)	
Low (IMS 1–2)	43 (31)
Moderate (IMS 3–5)	71 (51)
High (IMS 6–10)	25 (18)
Continuous renal replacement therapy, n (%)	14 (10)
Mechanically ventilated, n (%)	39 (28)
Adverse events, n (% of mobilisation episodes)	15 (7.8)
Death	0 (0)
Loss of consciousness	0 (0)
Fall to the ground	0 (0)
Cardiac arrest	0 (0)
Unplanned extubation	0 (0)
Removal of invasive lines and tubes	0 (0)
New onset of dysrhythmia	1 (0.5)
Hypotension necessitating escalation of therapy	14 (7.3)

ICU = intensive care unit; IMS = ICU mobility score; IQR = interquartile range.
Each vasoactive mobilisation day could contain more than one episode of mobilisation.

instability (57/232, 25%; Table 5). The main physiological limitations were haemodynamic (25/57) and cardiovascular instability (21/57). The reason for not mobilising was "unknown" in 24% of cases, reflecting a lack of specific documentation by staff at the time of mobility assessment.

Table 5
Reported reasons for not mobilising, n (%).

Physiological instability	57 (25)
Haemodynamic instability	25
Cardiovascular instability	21
Respiratory instability	8
Neurological instability	3
Medical orders	22 (10)
Low GCS	17 (7)
Patient refusal	16 (7)
Vasoactive therapy outside PT staff hours	17 (7)
Medical procedures	14 (6)
Sedated	12 (5)
Agitated	10 (4)
Palliation	6 (3)
CRRT device complications	3 (1)
Other	3 (1)
Unknown	55 (24)
Total	232 (100)

GCS = Glasgow Coma Score; PT = physiotherapy; CRRT = continuous renal replacement therapy.

By fitting a generalised linear mixed model, several factors associated with increased likelihood of mobilisation were identified (Table 6). A higher probability of mobilisation was associated with low (OR = 5.50, 95% CI = 2.23–13.59) and moderate dose (OR = 2.50, 95% CI = 0.95–6.59) vasoactive therapy, relative to high dose. Patients were almost three times more likely to mobilise on the second day (OR = 2.84, 95% CI = 1.74–4.65) of vasoactive therapy during an admission and twice as likely on the third day (OR = 2.166, 95% CI = 1.27–3.71), compared to the first day. No statistically significant associations were found between age, APACHE II, and gender and likelihood of mobilisation.

The distribution of profession leading mobilisation is described in Fig. 1. The majority of mobilisation episodes were led by nursing staff (64% vs 36%). Of all nurse-led mobilisation episodes, 41% were passive bed-to-chair sling transfers (IMS = 2) and 58% were active bed-to-chair transfers (IMS = 5). Patients achieved active out-of-bed mobility (IMS >3) in 59% of nurse-led episodes and 70% of physiotherapist-led episodes. Twenty-five patients mobilised by physiotherapists (36% of episodes) were ambulated (16 [22%] marched on the spot, 9 [13%] ambulated away from the bedspace), while no patients mobilised by nursing staff were ambulated (IMS 6–10).

3.3. Adverse events

In 195 episodes of mobilisation, the adverse event rate was 7.8% (n = 15). There were no serious adverse events associated with mobilisation. There was one occurrence of cardiac dysrhythmia (increasing number of ventricular ectopic beats) requiring no subsequent medical intervention and 14 occurrences of transient hypotension requiring escalation of vasoactive infusion dose (Table 4). All occurrences of hypotension were reversed with temporary increases in vasoactive drug dosage (usually < 10 min duration) which required no further medical intervention.

Early cessation of mobilisation occurred during 10 episodes (5.1%) as a result of transient physiological changes (SpO_2 desaturation to 88% and 90% [n = 2], hypotension [n = 4]), bradycardia [n = 1], nausea and vomiting [n = 1], a positional cuff leak [n = 1], and agitation [n = 1]). Desaturation was immediately corrected with increased FiO_2 or deep breaths, while the occurrences of hypotension and bradycardia recovered spontaneously with rest.

Patients who were more likely to experience an adverse event were those with lower mean arterial pressure (OR = 0.72, 95% CI = 0.58–0.88; Fig. 2), higher SpO_2 (OR = 1.83, 95% CI = 1.11 to 3.10) and higher FiO_2 (OR = 1.38, 95% CI = 1.10–1.72; see Table 7).

Table 6
Factors associated with delivery of mobilisation in patients receiving vasoactive therapy.

Factors	Mobilised (n = 139)	Not mobilised (n = 232)	Analysis	
			Odds ratio (OR)	*p* value
Age, mean (SD)	70 (11)	68 (11)	1.02	0.06
Male, n (%)	71 (51)	134 (58)	0.74	0.13
APACHE II, mean (SD)	20 (7)	22 (7)	0.99	0.27
Vasoactive infusion dosage, n (%)				
Low[a]	126 (44)	159 (55)	5.50	<0.001
Moderate[a]	11 (22)	40 (78)	2.50	0.06
High	2 (6)	33 (94)		
Day of vasoactive therapy, n (%)				
Day 1	20 (20)	79 (80)		
Day 2[b]	42 (49)	44 (51)	2.84	<0.001
Day 3[b]	23 (42)	32 (58)	2.17	0.005
Day 4[b]	9 (29)	22 (71)	1.25	0.50
Day 5–9[b]	33 (45)	40 (55)	2.28	0.003
Day 10+[b]	12 (44)	15 (56)	2.07	0.08

APACHE II = acute physiology and chronic health evaluation II score; SD = standard deviation.
[a] Describes OR and *p* value for a mobilisation episode relative to high vasoactive infusion dosages.
[b] Describes OR and *p* value for a mobilisation episode relative to day 1 of vasoactive therapy.

No statistically significant relationships were found for age, gender, disease severity, intensity of mobilisation (on the IMS), the presence of mechanical ventilation or continuous renal replacement therapy, profession leading mobilisation, or vasoactive drug dosage.

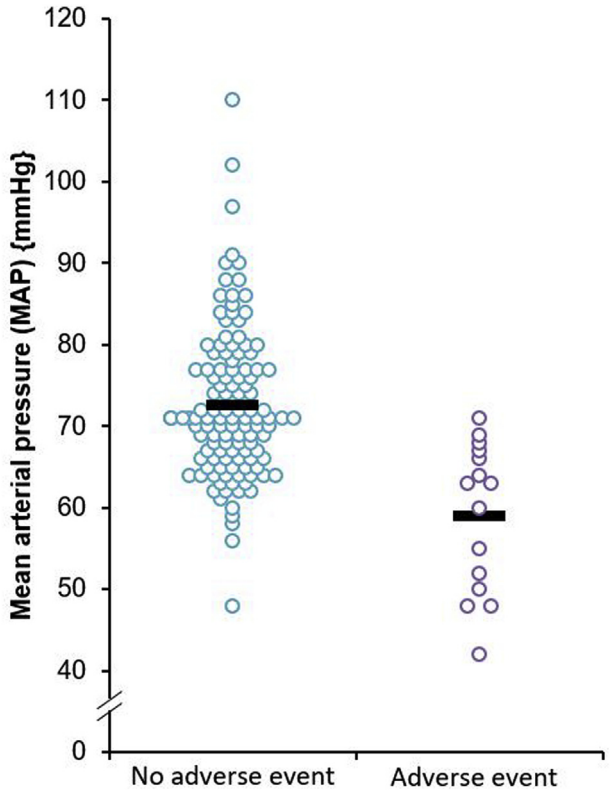

Fig. 2. Mean arterial pressure (MAP) for ICU patients who experienced no adverse event compared to those who experienced an adverse event during mobilisation. Mean values for each group are denoted by the horizontal line.

4. Discussion

This is the first study to investigate early mobilisation in a heterogeneous cohort of ICU patients receiving vasoactive drug support, and the main finding was that patients were safely mobilised on approximately one-third of vasoactive days, with a low rate of adverse events. The nature of those adverse events was minor as all, but one event (14/15) was related to transient occurrences of hypotension managed with increased titrations of vasoactive infusions.

Few studies of early mobilisation have included patients undergoing vasoactive therapy.[5,32] In one study by Hickman et al.,[32] 34% of all patients mobilised were on vasoactive drugs, and the average noradrenaline dose was 0.10 μg/kg/min (95% CI = 0.09–0.11 μg/kg/min; low dose according to our study). In

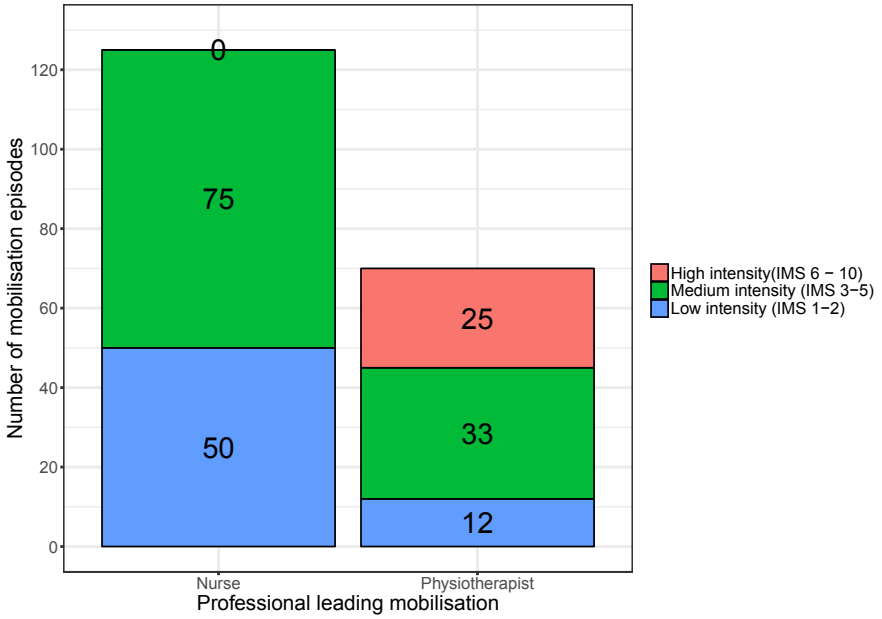

Fig. 1. Distribution of mobilisation frequency and intensity received by patients undergoing vasoactive therapy between physiotherapists and nurses. Mobilisation intensity was measured on the ICU mobility scale (IMS) and was categorised into low, moderate and high intensities.

Table 7
Factors associated with adverse events during episodes of mobilisation in patients receiving vasoactive therapy.

Factors	No adverse event (n = 180)	Adverse event (n = 15)	Analysis	
			Odds ratio	*p* value
Age, mean (SD)	70 (11)	69 (11)	1.02	0.69
Male, n (%)	66 (53)	6 (40)	4.45	0.31
APACHE II, mean (SD)	21 (7)	18 (6)	0.83	0.09
Continuous renal replacement therapy, n (%)	14 (11)	0 (0)		
Mechanical ventilation, n (%)	36 (29)	3 (20)	11.24	0.14
Higher dosage vasoactive infusion[a], n (%)	11 (9)	2 (13)	1.64	0.81
Physiological variables at time of mobilisation, mean (SD)				
Heart rate [bpm]	89 (18)	82 (18)	0.95	0.19
Mean arterial pressure [mmHg]	72 (11)	59 (9)	0.72	0.002
Respiratory rate [bpm]	19 (6)	17 (5)	1.03	0.85
Blood oxygen saturation (SpO_2) [%]	96 (3)	98 (2)	1.83	0.02
Fraction of inspired oxygen	0.31 (0.07)	0.30 (0.07)	1.38	0.005
Professional leading mobilisation, n (%)				
Nurse-led episodes	120 (96)	5 (4)	0.04	0.08
Physiotherapist-led episodes	75 (88)	10 (12)	0.46	0.61

APACHE II = acute physiology and chronic health evaluation II score; SD = standard deviation.
[a] "Higher dosage" includes moderate and high vasoactive infusion dosages; describes OR and *p* value for an adverse event relative to low infusion dosage.

contrast, our sample featured mobilisation for 22% of patients on moderate doses and 6% of patients on high doses of vasoactive therapy. Thus, our study captured a broader spectrum of vasoactive agents and higher doses of vasoactive therapy, which may be more useful to clinicians around the world where prescription of vasoactive agents can vary.

Our study is also one of the first to distinguish between physiotherapist-led and nursing-led mobilisation. Not surprisingly, all high intensity mobility (IMS 6–10) was led by physiotherapists. Rarely did nurses mobilise a patient to higher intensities than physiotherapists. However, the vital part that nurses have to play in the provision of mobilisation is highlighted by the number of mobilisation episodes carried out by nurses compared to physiotherapists. Nurse-led mobilisation was almost double that of physiotherapists (64% vs 36%) and most commonly consisted of bed-to-chair transfers (IMS 5). In our unit, the patient experience of mobilisation is genuinely multidisciplinary, with physiotherapists initiating progress and nurses carrying out the bulk of mobilisation.

Compared with other observational studies of mobilisation in ICU,[2,15,32] our adverse event rate was relatively high at 7.8%. However, the definition of an adverse event during mobilisation varies widely between studies. In particular, the inclusion of hypotension as an adverse event is not consistent. For example, some studies define adverse events relating to hypotension according to cut-off values for mean arterial pressure and systolic blood pressure[2,4,6] while others contend that hypotension itself is not adverse unless it results in loss of consciousness or falls.[5,35] Even in studies that include patients on vasoactive therapy,[5,32] there was only one study[32] which defined hypotension as an adverse event. Given the perceived risk of instability that typically causes clinicians to refrain from mobilising patients on vasoactive medications, we decided *a priori* to capture hypotension as an adverse event with the purpose of providing data to guide clinical reasoning. Our analysis of adverse events may therefore be conservative.

Accepting the heterogeneity in definition of adverse events, previous studies of mobilisation that included patients on low dose vasoactive therapy featured adverse event rates less than 1%.[5,32] Our study had an adverse event rate much higher at 7.8% but differs from these studies primarily in that our entire cohort consisted of vasoactive dependent patients and thus captured the rate for a higher risk subset of the ICU population. Furthermore, our adverse event rate was almost entirely attributable to episodes of reversible hypotension, which most experienced ICU physiotherapists would regard as clinically insignificant in the course of usual practice. Thus, despite a somewhat higher incidence of adverse events in our study, this rate is acceptable given the clinical insignificance of these events. Future studies should explore whether short-term variations in vasoactive therapy have any impact on longer term outcomes in ICU patients.

In our cohort, patients on low levels of therapy were five times more likely to be mobilised as those on high dose, while patients were twice as likely to be mobilised on moderate doses compared to high doses of vasoactive therapy. Given this relationship, it may be tempting for clinicians to apply this to their practice as a general rule and be disinclined to mobilise patients on moderate to high doses. However, many patients on moderate doses in our cohort benefited from mobilisation. In fact, a select few patients on high dosages were able to mobilise safely. These exceptions to our data emphasise that there may be many factors other than vasoactive drug dose influencing suitability for mobilisation. The relationships found might help to guide decision-making, however should not replace the process of clinical reasoning which encompasses the myriad factors not captured in our data.

In patients who were mobilised, adverse events were significantly more likely to occur in those with higher peripheral capillary oxygen saturations (SpO_2), higher fraction of inspired oxygen (FiO_2) and lower MAPs during mobilisation. While this may seem paradoxical, it may be that clinicians are more likely to attempt mobilisation in patients with higher SpO_2 as they presume they have adequate respiratory reserve. However, the statistically significant finding that SpO_2 and FiO_2 are predictors of adverse events in this cohort may not be clinically relevant, as the difference between SpO_2 of 98 and 96%, or FiO_2 of 0.30 and 0.31, would not be considered important by most clinicians. Notably, the statistically significant difference in MAP is clinically significant (72 vs. 59 mmHg) and consistent with the nature of adverse events experienced. We suggest that this parameter is more likely to influence the clinical reasoning process regarding risks of mobilisation in this cohort.

Our findings support the latest expert consensus statement[20] that vasoactive therapy is not an absolute contraindication to mobilisation. It is important to acknowledge that we have a carefully selected subgroup where the clinician has already excluded those perceived to be unstable, and thus we should be cautious in drawing conclusions about the broader safety of mobilising patients on high dose vasoactive agents. Nonetheless, it appears that the level of vasoactive support may not be an absolute indicator of safety to mobilise.

4.1. Limitations

This was a single centre study conducted in an Australian ICU with a strong mobilisation culture, and our findings may not be easily extrapolated to other ICUs with different practices (e.g. unit culture and sedation management). Therefore, replication of this study should be conducted across multiple local and international centres to test the consistency of our findings. Moreover, replication is only feasible in ICUs with electronic health records which allow detailed and time-sensitive data collection.

The conclusions drawn are also dependent on the accuracy of documentation in the electronic health record. However, to maximise accuracy, timing of documentation in the health record was cross-referenced with hourly nursing observation charts. Another potential source of error in this analysis is the capture of vital sign information immediately prior to the mobilisation episode, as this was not consistently reported in the physiotherapy or nursing documentation and was frequently inferred from the most recent automatic data importation. While in this retrospective analysis, we were limited by the data available; future prospective studies could ensure real-time measurement of vital signs throughout mobilisation to better clarify the relationships between vital signs and mobilisation response. Furthermore, we only captured adverse events that occurred at the time of mobilisation. Thus, we are unable to comment on longer term adverse events or clinical outcome for those in our sample who were mobilised.

The lack of documentation of a reason not to mobilise in 24% of cases is another limitation. As multidisciplinary focus on the importance of mobilisation increases, diligence with documentation of this parameter may improve in future studies.

Finally, the generalised linear mixed models used in our analysis to assess for relationships between variables are dependent on sample size. Given our small sample and few adverse events (particularly in the high dosage group), it is possible that our study was underpowered for these relationships and thus unable to detect small effect sizes. Since we have shown that safe mobilisation is possible even in some with moderate to high drug doses, there is a need for future studies to investigate which factors other than dosage determine suitability of moderate to high dose patients for mobilisation.

5. Conclusion

In our ICU, patients were mobilised on approximately one-third of vasoactive days. Those receiving low levels of support were most likely to mobilise, and the risk of adverse events during mobilisation was small (7.8%) and almost entirely due to reversible hypotension. Patients receiving vasoactive therapy may be at a relatively higher risk of experiencing hypotension during mobilisation, but in our cohort, this was anticipated and managed with transient escalation of vasoactive therapy. Clinicians working in ICU should not consider vasoactive therapy an absolute contraindication to mobilisation.

Acknowledgements

The authors gratefully acknowledge the staff of the Intensive Care Unit of Canberra Hospital for their support in contributing to this data set.

Supplementary information

Supplementary data related to this article can be found at https://doi.org/10.1016/j.aucc.2018.03.004.

References

[1] Stiller K. Physiotherapy in intensive care: an updated systematic review. Chest 2013;144(3):825–47.
[2] Hodgson C, Bellomo R, Berney S, Bailey M, Buhr H, Denehy L, et al. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. Crit Care 2015;19:81.
[3] Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373(9678):1874–82.
[4] Hodgson CL, Bailey M, Bellomo R, Berney S, Buhr H, Denehy L, et al. A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU. Crit Care Med 2016;44(6):1145–52.
[5] Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 2008;36(8):2238–43.
[6] Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. Intensive Care Med 2015;41(5):865–74.
[7] Morris PE, Griffin L, Berry M, Thompson C, Hite RD, Winkelman C, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. Am J Med Sci 2011;341(5):373–7.
[8] Rydingsward JE, Horkan CM, Mogensen KM, Quraishi SA, Amrein K, Christopher KB. Functional status in ICU survivors and out of hospital outcomes: a cohort study. Crit Care Med 2016;44(5):869–79.
[9] Berney SC, Harrold M, Webb SA, Seppelt I, Patman S, Thomas PJ, et al. Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study. Crit Care Resusc 2013;15(4):260–5.
[10] Jolley SE, Moss M, Needham DM, Caldwell E, Morris PE, Miller RR, et al. Point prevalence study of mobilization practices for acute respiratory failure patients in the United States. Crit Care Med 2017;45(2):205–15.
[11] Harrold ME, Salisbury LG, Webb SA, Allison GT. Early mobilisation in intensive care units in Australia and Scotland: a prospective, observational cohort study examining mobilisation practises and barriers. Crit Care 2015;19:336.
[12] Nydahl P, Ruhl AP, Bartoszek G, Dubb R, Filipovic S, Flohr HJ, et al. Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. Crit Care Med 2014;42(5):1178–86.
[13] Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, et al. Vasopressors for hypotensive shock. Cochrane Database Syst Rev 2016 Feb 15;2: CD003709. https://doi.org/10.1002/14651858.CD003709.pub4.
[14] Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med 2009;37(9):2499–505.
[15] Berney S, Haines K, Skinner EH, Denehy L. Safety and feasibility of an exercise prescription approach to rehabilitation across the continuum of care for survivors of critical illness. Phys Ther 2012;92(12):1524–35.
[16] Winkelman C, Johnson KD, Hejal R, Gordon NH, Rowbottom J, Daly J, et al. Examining the positive effects of exercise in intubated adults in ICU: a prospective repeated measures clinical study. Intensive Crit Care Nurs 2012;28(6):307–18.
[17] Needham DM, Korupolu R, Zanni JM, Pradhan P, Colantuoni E, Palmer JB, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. Arch Phys Med Rehabil 2010;91(4):536–42.
[18] Bailey P, Thomsen GE, Spuhler VJ, Blair R, Jewkes J, Bezdjian L, et al. Early activity is feasible and safe in respiratory failure patients. Crit Care Med 2007;35(1):139–45.
[19] Sommers J, Engelbert RH, Dettling-Ihnenfeldt D, Gosselink R, Spronk PE, Nollet F, et al. Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. Clin Rehabil 2015;29(11):1051–63.
[20] Hodgson CL, Stiller K, Needham DM, Tipping CJ, Harrold M, Baldwin CE, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. Crit Care 2014;18(6):658.
[21] Leditschke IA, Green M, Irvine J, Bissett B, Mitchell IA. What are the barriers to mobilizing intensive care patients? Cardiopulm Phys Ther J 2012;23(1):26–9.
[22] Green M, Marzano V, Leditschke IA, Mitchell I, Bissett B. Mobilization of intensive care patients: a multidisciplinary practical guide for clinicians. J Multidiscip Healthc 2016;9:247–56.
[23] Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper DJ, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358(9):877–87.
[24] Brown SM, Lanspa MJ, Jones JP, Kuttler KG, Li Y, Carlson R, et al. Survival after shock requiring high-dose vasopressor therapy. Chest 2013;143(3):664–71.
[25] Natalini G, Schivalocchi V, Rosano A, Taranto M, Pletti C, Bernardini A. Norepinephrine and metaraminol in septic shock: a comparison of the hemodynamic effects. Intensive Care Med 2005;31(5):634–7.
[26] Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med 2008;34(12):2226–34.
[27] Investigators TA, Group tACT. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371(16):1496–506.
[28] Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015;372(14):1301–11.
[29] Hollenberg SM. Vasoactive drugs in circulatory shock. Am J Respir Crit Care Med 2011;183(7):847–55.
[30] Hodgson C, Needham D, Haines K, Bailey M, Ward A, Harrold M, et al. Feasibility and inter-rater reliability of the ICU Mobility Scale. Heart Lung 2014;43(1):19–24.

[31] Tipping CJ, Bailey MJ, Bellomo R, Berney S, Buhr H, Denehy L, et al. The ICU mobility scale has construct and predictive validity and is responsive. A multicenter observational study. Ann Am Thorac Soc 2016;13(6):887–93.
[32] Hickmann CE, Castanares-Zapatero D, Bialais E, Dugernier J, Tordeur A, Colmant L, et al. Teamwork enables high level of early mobilization in critically ill patients. Ann Intensive Care 2016;6(1):80.
[33] Note for guidance on clinical safety data management: definitions and standards for expedited reporting. Canberra: Therapeutic Goods Administration; 2000. CPMP/ICH/377/95, https://www.tga.gov.au/publication/note-guidance-clinical-safety-data-management-definitions-and-standards-expedited-reporting.
[34] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818–29.
[35] Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. Crit Care 2013;17(4):R156.