Incidence and Outcomes of Prolonged Acute Mechanical Ventilation of Surgical Patients in Academic Hospitals

Onuma Chaiwat MD*,
Kaweesak Chittawatanarat MD**, Annop Piriyapathsom MD*,
Chawika Pisitsak MD***, Suneerat Kongsayreepong MD*

** Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*
**** Department of Anesthesiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Objective: *To identify incidence, outcomes and risk factors of prolonged acute mechanical ventilation (PAMV) in surgical patients admitted to surgical intensive care units (ICUs) of two large academic hospitals in Thailand.*
Material and Method: *This is a retrospectively analyses of the THAI-SICU database which is a multi-center, prospective, observational cohort study to identify the adverse events and mortality in surgical ICUs. The new term PAMV was defined as the requirement of mechanical ventilation for longer than 4 days.*
Results: *A total of 1,084 patients were included in this study. The incidence of PAMV in this cohort was approximately 40%. PAMV patients demonstrated significantly higher percentage of clinical complication including stroke, seizure, sepsis, upper gastrointestinal hemorrhage, acute kidney injury and adult respiratory distress syndrome (ARDS)/acute lung injury (ALI) than patients who required mechanical ventilation <4 days. Sepsis, non-operative and controlled mechanical ventilation on admission were identified as independent risk factors for PAMV. Patients who had sepsis were 3.2 times higher risk associated with PAMV (adjusted odds ratio (OR) 3.25, 95% confidence interval (CI) 2.25 to 4.7) and patients who were non-operative and on controlled mechanical ventilation (CMV) on admission were approximately 2.5-fold higher risk associated with PAMV.*
Conclusion: *The incidence of PAMV was 40% in surgical ICU patients. The mortality and complication rate were higher in PAMV patients.*

Keywords: *Prolonged mechanical ventilation, Acute, Surgical patients, Intensive care unit, Mortality*

J Med Assoc Thai 2017; 100 (Suppl. 7): S20-S27
Full text. e-Journal: *http://www.jmatonline.com*

Mechanical ventilation is the leading intervention applied to the patients in intensive care units (ICUs). In the previous study, it was estimated that more than half of patients admitted to ICUs required acute mechanical ventilation[1]. Thereafter, if the patient does not fully recover from the acute episode, the transition to chronic critical illness syndrome (CCIS) will occur and may result in the need of prolonged mechanical ventilation (PMV). Originally, PMV has been defined as the requirement of at least six hours of mechanical ventilation per day for at least 21 consecutive days[2]. While in a 1998 international survey showed that the mean duration of mechanical ventilation was approximate 10 days[3], more recent data from the United States demonstrated that the majority of critically ill patients needed mechanical ventilation in between 3 and 4 days[4]. Accordingly, the new term "prolonged acute mechanical ventilation" (PAMV) was emerged and defined as the requirement of mechanical ventilation for longer than 4 days[5].

The number of PAMV patients in the United State was approximately 300,000 individual each year and it has been projected to be more than double in the year 2020[5]. Moreover, 3 to 7% of unweaned PAMV patients will survive and remain chronically ill and require mechanical ventilation longer than 21 days that originally characterize as PMV[2]. Such patients showed numerous problems especially the consumption of a significant amount of health-care resources. The data from the Nationally representative sample of U.S. hospital discharges demonstrated that PAMV patients had higher length of hospital stay and hospital costs, although, the actual mortality were similar between the two groups[5]. However, the previous study[5] regarding the incidence and outcomes of PAMV was a cross

Correspondence to:
Chaiwat O, Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone +66-2-4197990, Fax +66-2-4113256
E-mail: onuma27@hotmail.com

sectional study using the hospital discharges data. The present study will retrospectively analyze the cohort of the multicenter Thai University-Based Surgical Intensive Care Unit (THAI-SICU) Study[6] database in two academic centers (Siriraj Hospital and Maharaj Nakhon Chiang Mai Hospital). The aims of the present study were to determine the incidence, risk factors and outcomes of PAMV in surgical patients admitted to surgical ICUs in two academic hospitals. In THAI-SICU Study, the median duration of mechanical ventilation was around 2 days and 5 days in patients who did not develop acute respiratory distress syndrome (ARDS) and in patients who had ARDS, respectively[7]. Consequently, using 4 days as a cuff off value has a clinical relevance given that it estimates the average duration of mechanical ventilation in Thai surgical patients.

Material and Method

The THAI-SICU study[6] was a multi-center, prospective, observational cohort study including nine-university-based surgical ICUs covering all regions across the country, between April, 2011 and January, 2012. Basically, the objectives of the THAI-SICU study were to identify the adverse events and mortality in SICUs. The study proposals and all case record forms were approved by the Thailand Joint Research Ethics Committees (JREC, No. 001/2011) or by Ethics Committee (EC) or by Institutional Review Board (IRB) of individual institution prior to collect the data. All patients or relatives were provided informed consent before gathering information. The present study was retrospectively analyzed the THAI-SICU database in Siriraj and Maharaj Nakhon Chiang Mai Hospitals.

All adult surgical patients over the age of 18, who were admitted to the general SICUs during the study period, were recruited. The investigators excluded those patients who were moribund cases, had ICU stay less than 6 hours, non-surgical patients, cardiac and neuro-surgery patients and the foreigners. This study would exclude factors in addition to the THAI-SICUs study including the patients who died in the first 24 hours, who were admitted less than 24 hours and who did not require mechanical ventilators. The present study was primarily designed to identify the incidence and outcomes of PAMV, which defined as the requirement of mechanical ventilation for longer than 4 days in critically ill surgical patients. The primary outcomes were the incidence of PAMV and all causes 28 day mortality. Secondary outcomes were the independents risk factors associated with PAMV. The data collection were divided into 3 parts including "on admission", "daily recording data", and "at discharge". The information of patients' characteristic, co-morbid diseases, ventilator data, adverse events and outcomes were initially collected at the time of admission and throughout the ICU stay or up to 28 days of ICU admission. The patients were followed until 28 days after ICU discharge if they still survived. The detail of data collection was described in previous study[6].

Statistical analysis

Incidence of PAMV was reported in percentages. Continuous data was presented as mean ($\pm$SD) or median with interquartile range (IQR) for variables with normal or non-normal distribution respectively. Categorical data was reported as numbers and percentages. Univariable analysis was used to detect the differences between patients with and without PAMV. Student t-test and the Mann-Whitney U test were used for continuous variables whereas Chi-square or Fisher exact test for categorical variables. To determine effect of each factor on PAMV after adjusting for others, all variables that were statistically significant and clinical relevant with univariable p-value ≤ 0.2 were entered in multiple logistic regression analysis. The entered variables included age, priority of admission, American Society of anesthesiologist classification >2, Acute Physiology And Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) scores, underlying diseases, hemoglobin and albumin levels, surgical data and ventilator data. Adjusted odds ratios of PAMV are reported along with their 95% CIs. Statistical significance was defined as $p<0.05$. STATA, version 11.0 (STATA Inc., College Station, TX) was used for statistical analysis.

Results

A total 1,778 surgical patients were enrolled (977 patients from Siriraj Hospital and 801 patients from Maharaj Nakhon Chiang Mai Hospitals). Of these 1,778 patients, 1,101 (62%) patients required mechanical ventilators. 17 patients were further excluded from dead within the first 24 hours and the duration of ICU admission less than 24 hours. Thereafter, 1,084 patients were included in the analysis. There were 430 patients needed mechanical ventilation equal and greater than 96 hours. Consequently, the incidence of PAMV in this cohort was approximately 40% (Fig. 1). Table 1 compared the baseline characteristics in terms of patient's data,

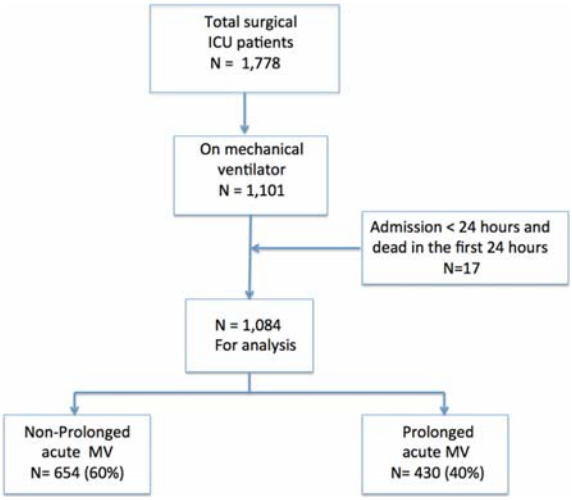

Fig. 1 Outline of the cohort.

disease's severity, co-morbid diseases, specific laboratory data, surgical data and ventilator data between non-PAMV and PAMV patients. The patients who had PAMV were significantly older and had higher severity on admission. The APACHE II score and SOFA score on admission were significantly higher in PAMV patients, 16 vs. 11 and 5 vs. 3, $p<0.01$ respectively. In addition, the proportion of ASA >2 in PAMV patients were significantly higher than in patients who did not experience PAMV, 87% vs. 66%, $p<0.01$. For the co-morbid disease, the PAMV patients had significantly higher percentage of congestive heart failure, vascular disease, previous stroke and chronic obstructive pulmonary disease (COPD) compared with non- PAMV patients. Lower hemoglobin and albumin levels were demonstrated in PAMV patients. Moreover, there were significantly higher number of patients who had hemoglobin <8 g/dL and albumin <2.5 g/dL in PAMV group than in non-PAMV group. PAMV patients showed significantly higher amount of non-operation and emergency surgery ($p<0.01$) than non-PAMV patients. Controlled mechanical ventilator mode (CMV) on admission was used in higher percentage in PAMV group compared to non- PAMV group (90% vs. 64%, $p<0.01$).

During the ICU stay, PAMV patients demonstrated significantly higher percentage of clinical complication including stroke, seizure, sepsis, upper gastrointestinal hemorrhage, acute kidney injury and acute respiratory distress syndrome/acute lung injury (ARDS/ALI) than patients who required mechanical ventilation <4 days as shown in Table 2. With regard to the clinical outcomes, ventilator days, ICU length of stay, hospital length of stay were significantly longer in PAMV patients than in non-PAMV patients. In addition, PAMV patients showed significantly higher 28-day mortality rate compared to non-PAMV patients (27% vs. 13%, $p<0.01$).

Table 3 demonstrated the clinical predictors of the PAMV in final logistic model. The adjusted variables were previously mentioned. Sepsis, non-operative and the patients who were on controlled mechanical ventilation on admission were identified as independent risk factors for PAMV. Patients who had sepsis were 3.2 times higher risk associated with PAMV (AOR 3.25, 95% CI 2.25 to 4.7) and patients who were non-operative and on controlled mechanical ventilation (CMV) on admission were approximately 2.5-folds higher risk associated with PAMV (Table 3).

Discussion

The incidence of prolonged acute mechanical ventilation (PAMV) was reported 40% in this cohort of critically ill surgical patients. The clinical outcomes including ventilator days, ICU and hospital length of stay were longer and the mortality rate was doubled in PAMV patients. Previous retrospective cohort study[8] reported the incidence of PAMV was 26% among 94,553 patients receiving mechanical ventilation. The reported incidence of PAMV was much lower than our study. The majority of PAMV patients (60%) from this cohort were from mixed and cardiac ICUs that were not the same population as our study. Given that cardiac patients had a tendency to yield a shorter duration of mechanical ventilation because of lesser disease severity[9].

Another study from The United States (US)[5] using the adult hospital discharge information, 39% of the patients were categorized as PAMV according to ICD-9 code 96.72. Although PAMV subjects comprised only 39% of patients undergoing mechanical ventilation, they accounted almost 64% of all annual in-patient costs. Median hospital costs for PAMV patients were $40,903 as compared to $13,434 in non-PAMV patients. Not surprisingly, PAMV patients demonstrated a longer duration of hospital LOS and higher complication as reported in our study and others[8,10], resource utilization was absolutely much higher as compared to non-PAMV patients. Lee et al[10] retrospectively analyzed data from medical records on day 4 of mechanical ventilation in medical ICU, Korea, they found that PAMV patients represented 41.2% of all ventilated patients. Based on previous reports and ours, the incidence of PAMV patients was

Table 1. Comparison of patients' characteristics between PAMV and non-PMV patients

	PMV			
	All (n = 1,084)	No (n = 654)	Yes (n = 430)	*p*-value
Patient data				
Age	64 (52-75)	62 (51-74)	67.5 (54-77)	<0.01
BMI	21.9 (18.8-25.2)	21.9 (18.8-25)	22.0 (19.0-25.3)	0.82
Gender: Male	613 (56.6)	367(56.1)	246(57.2)	0.72
Priority of admission (Prioritization Model)#				
Priority 1 (Unstable patients)	406 (37.8)	203 (31.4)	203(47.7)	
Priority 2 (Require invasive monitoring)	616 (57.4)	421 (65.1)	195 (45.8)	
Priority 3 (Unstable but severe underlying disease	42 (3.9)	21 (3.3)	21(4.9)	<0.01
ASA III-V	805 (74.3)	433(66.2)	372 (86.5)	<0.01
APACHE II on admission	13 (9-19)	11(8-17)	16 (12-22)	<0.01
SOFA on admission	4 (2-7)	3 (1-5)	5 (3-8)	<0.01
Still Smoking	133 (12.3)	72 (11.0)	61 (14.2)	
Ex-smoking	288 (26.6)	177 (27.1)	111(25.8)	
None	663 (61.2)	405 (61.9)	258 (60.0)	0.30
Co-morbid diseases Hypertension	481 (44.4)	287 (43.9)	194 (45.1)	0.69
Coronary Artery Disease	90 (8.30)	50 (7.7)	40 (9.3)	0.33
Congestive Heart Failure	34 (3.1)	13 (2.0)	21 (4.9)	<0.01
Vascular disease	68 (6.3)	32 (4.9)	36 (8.4)	0.02
Previous stroke	57 (5.3)	28 (4.3)	29 (6.7)	0.08
Asthma	17 (1.6)	13 (1.99)	4 (0.9)	0.17
COPD	80 (7.4)	39 (6.0)	41 (9.5)	0.03
Diabetes Mellitus	229 (21.1)	137 (21.0)	92 (21.4)	0.86
Chronic renal failure	117 (10.8)	62 (9.5)	55 (12.8)	0.09
Malignancy	219 (20.20)	128 (19.57)	91(21.16)	0.52
Immune disease	16 (1.5)	13 (2.0)	3(0.7)	0.09
Organ transplantation	9 (0.8)	5 (0.8)	4 (0.9)	0.77
Hemoglobin on admission	10.1 (8.8-11.6)	10.4 (9.1-11.9)	9.7 (8.3-11)	<0.01
Hemoglobin <8 g/dL	152 (14.06)	74(11.37)	78 (18.14)	<0.01
Albumin on admission	2.5 (2-3)	2.55 (2-3.1)	2.4 (1.9-2.8)	<0.01
Albumin<2.5 g/dL	450 (47.4)	243 (43.2)	207 (53.5)	<0.01
Surgical data				
Emergency	386 (35.6)	219 (33.5)	167 (38.8)	
Elective	378 (34.9)	290 (44.3)	88 (20.5)	
Not define	55 (5.1)	43 (6.6)	12 (2.8)	
Not operation	265 (24.45)	102 (15.60)	163 (37.91)	<0.01
Upper-abdominal surgery	270 (24.91)	161 (24.62)	109 (25.35)	0.79
Lower-abdominal surgery	271 (25.00)	180 (27.52)	91 (21.16)	0.02
Peripheral vascular surgery	29 (2.68)	18 (2.75)	11 (2.56)	0.85
Thoracic	97 (8.95)	61 (9.33)	36 (8.37)	0.59
Other site surgery	47 (4.34)	29 (4.43)	18 (4.19)	0.84
Ventilator data (average first 7 days)				
CMV mode (PCV, VCV)	797 (74.00)	413 (63.54)	384 (89.93)	<0.01
SIMV mode	319 (30.50)	181 (27.85)	138 (34.85)	0.02
Maximum tidal volume, median(IQR)	530 (474-605)	500 (450-566)	591.5 (510-670)	<0.01

Data presented as number (%) or Median (IQR)
BMI = body mass index; ASA = American Society of Anesthesiologist classification; APACHE = Acute Physiology And Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; COPD = chronic obstructive pulmonary disease; CMV = controlled mechanical ventilation; SIMV = synchronized intermittent mandatory ventilation; PEEP positive end expiratory pressure
# Society of Critical Care Medicine. Crit care med 1999 Mar,27(3):633-38

Table 2. Complication and outcomes between PMV and non-PMV patients

Complications	PMV			
	All (n = 1,084)	No (n = 654)	Yes (n = 430)	*p*-value
Symptomatic DVT	5 (0.5)	2 (0.3)	3 (0.7)	0.35
Pneumonia	18 (1.7)	7 (1.1)	11 (2.6)	0.06
Stroke	4 (0.4)	0	4 (0.9)	0.01
Seizure	20 (1.9)	2 (0.3)	18 (4.2)	<0.01
Sepsis	434 (40.0)	145 (22.2)	289 (67.2)	<0.01
Upper GI hemorrhage	36 (3.3)	7 (1.1)	29 (6.7)	<0.01
Acute kidney injury	304 (28.0)	98 (15.0)	206 (47.9)	<0.01
ARDS/ALI	80 (7.4)	18 (2.8)	62 (14.4)	<0.01
Outcomes				
Ventilator days	3 (1-6)	1 (1-2)	8 (5-15)	<0.01
ICU LOS	4 (2-8)	2 (1-3)	10 (6-18)	<0.01
Hospital LOS	17 (11 to 29)	15 (9 to 23)	23 (15 to 37)	<0.01
28 day mortality	198 (18.3)	83 (12.7)	115 (26.7)	<0.01

Data presented as number (%) or median (IQR)
DVT = deep vein thrombosis; ARDS = Acute Respiratory Distress Syndrome; ALI = Acute Lung injury; ICU = intensive care unit; LOS = length of stay

Table 3. Independent risk factors for prolonged acute mechanical ventilator

	Adjusted odds ratio (95% CI)	*p*-value
Sepsis	3.25 (2.25 to 4.70)	<0.01
Non-operative	2.57 (1.50 to 4.38)	<0.01
Controlled mechanical ventilation	2.64 (1.70 to 4.20)	<0.01

approximately 30 to 40% of all mechanical ventilated patients. As previously mentioned[11], it was estimated that their volume will dramatically increase in the future and become an emerging challenge for the health care system.

The mortality rate of PAMV patients in this study was approximately 27% and was significantly higher than non-PAMV patients. Conversely, Zilberberg et al[5] found that even with higher coexisting conditions and complications including sepsis and ARDS, the hospital mortality for the PAMV group did not differ from that in the mechanical ventilator <96 hours group (35% vs. 34%, respectively). Additionally, recent study[10] from Korea reported the 28-day mortality rate in PAMV patients was 35% and demonstrated that lower body mass index, the need for vasopressors, the use of neuromuscular blocking agents and hemodialysis were associated with 28-day mortality in those without Do-Not-Resuscitate orders within 4 days. Recently, Dettmer et al[12] performed the systematic review to identify the prognostic factors that predicted long-term mortality (≥6 months) in patients who had been on mechanical ventilator >14 days. Six factors demonstrated strong strength of evidence associated with mortality including age, vasopressor requirement, thrombocy topenia, preexisting kidney disease, failed weaning and acute kidney injury ± hemodialysis requirement. For our study, apart from the mortality rate, we found that patients with PAMV showed significantly higher rate of sepsis, upper GI hemorrhage, acute kidney injury and ARDS than in non-PAMV patients. Acute kidney injury with or without hemodialysis seemed to be the main factor related to the poor outcome in patients who had prolonged mechanical ventilation.

Several risk factors regarding acute critical care course have been identified to be associated with the duration of mechanical ventilation including advanced age, APACHE II score[13,14], albumin level[13], shock on

admission[14,15], refractory acidosis[14], non-thyroidal illness syndrome[16], and renal dysfunction[17,18]. Previous study from Pan et al[19] showed that prolonged mechanical ventilation (>21 days) patients required a significantly longer length to reach the readiness for weaning. In addition, the investigators identified acute kidney injury on an initial mechanical ventilation day as an independent predictor for prolonged mechanical ventilation (>21 days) among ICU patients. Those previous results confirmed that ICU patients with renal dysfunction had a higher risk to prolong mechanical ventilation. In contrast to our study, in a univariate analysis, chronic renal failure as a co-morbid disease was not significantly different between PAMV and non-PAMV patients. However, we did not have the information regarding acute kidney injury before ICU admission, though we demonstrated that acute kidney injury occurred 3 times higher among PAMV group compared to non-PAMV group. Moreover, the definition of prolonged mechanical ventilation was different, our study used acute PMV while others used both originally definition (>21 days) or longer than 14 days. Consequently, the risk factors for PMV might vary. This study showed that sepsis on admission, non-operative patients and patients who were using CMV on admission were 3 factors independently associated with PAMV in surgical ICUs. Up to our knowledge, this is the first study in Thailand demonstrated the independence risk factors for PAMV in critically ill surgical patients. Patients who had sepsis and/or on mechanical ventilation on ICU admission trended to have higher severity of disease and prolong mechanical ventilation. Although, it was unclear whether non-operative patients were associated with PAMV, non-operative patients admitted to surgical ICUs frequently had many medical problems or un-operated conditions that lead to prolong ICU stay and absolutely prolong mechanical ventilation.

Some limitation should be addressed. Firstly, this study was an observational retrospective analysis, some parameters for instance pre-admission acute kidney injury, weaning parameters could not be recovered and the observational design itself was intrinsically prone to bias. Secondly, our study did not identify intra-operative variables that could be risk factors for PAMV for example intraoperative blood loss and the respiratory complication. Thirdly, the chosen cut off points for PAMV (>96 hours) limited the ability to compare the literature findings. Finally, our data represented the experience of academic centers and reflect a unique organization, the results of this study may not be generalizable to other different systems even in Thailand. Further research is needed to identify peri-operative factors that affect the duration of mechanical ventilation among surgical ICU patients.

Conclusion

The incidence of prolonged acute mechanical ventilation was 40% among critically ill surgical patients in two largest academic hospitals in Thailand. The clinical outcomes including ventilator days, ICU and hospital length of stay were longer and the mortality rate was doubled in PAMV patients. PAMV patients demonstrated significantly higher percentage of clinical complication including stroke, seizure, sepsis, upper gastrointestinal hemorrhage, acute kidney injury and ARDS/ALI. Sepsis on admission, non-operative patients and patients who were using CMV on admission were 3 factors independently associated with PAMV in surgical ICUs. Early identification of high-risk patients for PAMV and consider early intervention might help to decrease complication and costs related to this patient population.

What is already known on this topic?

The incidence of prolonged acute mechanical ventilator was high among ICU patients. The clinical outcome including mortality and complication were higher in PAMV patients.

What this study adds?

Sepsis on admission, non-operative patients and patients who were using CMV on admission were 3 factors independently associated with PAMV in surgical ICUs. Early identification of high-risk patients for PAMV and consider early intervention might help to decrease complication and costs related to this patient population.

Acknowledgements

The authors would like to thank Kamonpan Homchuangsub for her assistance in preparing this manuscript.

Trial registration

Clinicaltrials.gov; NCT 01354197.

Potential conflicts of interest

None.

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อุบัติการณ์และผลลัพธ์ของการใช้เครื่องช่วยหายใจมากกว่า 4 วัน ในผู้ป่วยวิกฤตศัลยกรรม โรงพยาบาลมหาวิทยาลัย

อรอุมา ชัยวัฒน์, กวีศักดิ์ จิตตวัฒนรัตน์, อรรณพ พิริยะแพทย์สม, ชวิกา พิสิฏฐศักดิ์, สุณีรัตน์ คงเสรีพงศ์

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์ผลลัพธ์และปัจจัยเสี่ยงของการใช้เครื่องช่วยหายใจนานมากกว่า 4 วัน Prolonged acute mechanical ventilation (PAMV) คือคำจำกัดความใหม่ที่หมายถึงระยะเวลาการใช้เครื่องช่วยหายใจนานกว่า 4 วัน*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาแบบย้อนหลังในฐานข้อมูลการศึกษาสหสถาบันในหออภิบาลผู้ป่วยหนักทางศัลยกรรมของโรงพยาบาลมหาวิทยาลัยในประเทศไทย (THAI-SICU) ในสองสถาบันประชากรที่เข้าศึกษาคือ ผู้ป่วย ศัลยกรรมอายุมากกว่า 18 ปี ที่เข้ารับการรักษาในหออภิบาลผู้ป่วยหนักทางศัลยกรรม*

ผลการศึกษา: *อุบัติการณ์ของ PAMV อยู่ที่ร้อยละ 40 ผู้ป่วย PAMV มีอัตราการตายและภาวะแทรกซ้อนเช่น หลอดเลือดสมองอุดตัน ชัก ติดเชื้อเลือดออกจากทางเดินอาหารส่วนต้น ภาวะไตบกพร่องและภาวะปอดอักเสบสูงกว่าผู้ป่วยที่ไม่มี PAMV อย่างมีนัยสำคัญทางสถิติ ภาวะติดเชื้อผู้ป่วยที่ไม่ได้รับการผ่าตัดและการใช้เครื่องช่วยหายใจแบบ controlled mechanical ventilation เป็นปัจจัยเสี่ยงที่สำคัญของ PAMV ในผู้ป่วยวิกฤตศัลยกรรม*

สรุป: *อุบัติการณ์ของการใช้เครื่องช่วยหายใจนานกว่า 4 วันในผู้ป่วยวิกฤตศัลยกรรมในโรงพยาบาลมหาวิทยาลัยอยู่ที่ร้อยละ 40 อัตราการตายและภาวะแทรกซ้อนพบได้ในอัตราสูงกว่าผู้ป่วยที่มีระยะเวลาการใช้เครื่องช่วยหายใจสั้นกว่า*