Treatment with Vasoactive Drugs and Outcomes in Surgical Critically Ill Patients: The Results from the THAI-SICU Study

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Objective: *The purpose of this study is to assess the impact of the use of vasoactive drugs on morbidity and mortality in surgical critically ill patients.*

Material and Method: *We conducted a multi-center prospective observational study in Thai university-based surgical intensive care units (SICU) over a 22-month period. Patient data were recorded by case record form in 3 main phases: admission, daily and discharge. Data collection included patient characteristics, pattern of vasoactive drugs use, and outcomes.*

Results: *Nine university-based SICU comprising 4,652 patients were included in the study. The vasopressor exposed patient group had 1,155 patients (24.8%). Either vasopressor or inotrope exposed group demonstrated significantly higher ICU mortality, 28-day mortality and new arrhythmia than the non-exposed group ($p<0.001$). In multivariable analysis, norepinephrine or epinephrine significantly increased risks of all unfavorable outcomes while dopamine significantly increased only new arrhythmia (OR 1.44; 95% CI 1.02-2.02, $p = 0.036$) in vasopressor-exposed patients. Epinephrine had the highest risk of all unfavorable outcomes with an OR 3.17; 95% CI 2.10-4.78, ($p<0.001$) for ICU mortality, OR 2.62; 95% CI 1.73-3.97, ($p<0.001$) for 28-day mortality, and OR of 1.77; 95% CI 1.13-2.75, ($p = 0.012$) for new arrhythmia. Neither dobutamine nor milrinone showed any significant results in inotrope exposed patients.*

Conclusion: *Vasoactive drug exposed patient groups had significantly higher incidence of new arrhythmia, ICU mortality, and 28-day mortality. Epinephrine exposure was associated with the highest risk of unfavorable outcomes. Further information from well-designed studies is needed to justify the most appropriate use of vasoactive drugs.*

Keywords: *Surgical ICU, Vasoactive drug, Vasopressor, Inotrope, ICU outcomes*

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Vasoactive drugs have been used routinely in critically ill patients to restore tissue perfusion when volume therapy cannot achieve the goals of shock resuscitation. In general, dopamine, norepinephrine, and epinephrine are used to achieve vasopressor effects and dobutamine is used for an inotropic effect[1,2]. Many pathological conditions can cause inadequate tissue perfusion to organs. Therefore, vasoactive drugs targeted for their therapeutic effects according to the mechanism of shock should result in the most favorable patient outcomes[3]. However, while applying the appropriate drug is necessary, it is also key to understand the optimal time for drug implementation as a delay in treatment can cause organ ischemia and failure[4]. Another interesting aspect of vasoactive drug application is dosage. Previous studies have shown that overuse of vasoactive drugs, especially vasopressors, can lead to unfavorable outcomes[5]. In addition to the improper use of vasoactive drugs, each drug may have undesirable effects causing unfavorable outcomes. For instance, the potential for immunosuppression[6,7], increased tachyarrhythmia[8,9], and increased mortality in a study of a European cohort of intensive care units[10] has been reported with the use of dopamine. The vasoconstrictive effect of epinephrine increase the risk of decreased blood flow to splanchnic organs[11]. The vasodilatory effects of

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dobutamine and milrinone can exacerbate hypotension and decrease organ perfusion pressure[12].

The role of vasoactive agents on the clinical outcomes has been debatable in previous studies[5-9]. In addition, there were several confounding factors involved in treatment outcomes. The aim of the study is to assess the impact of the use of vasoactive agents on morbidity and mortality, especially in surgical critically ill patients.

Material and Method

This is a prospective cohort observational study of data collected from THAI-SICU[13]. Data collection was performed at 9 university-based Surgical Intensive Care Units (SICU) from April 2011 to January 2013 over a period of 22 months. The subjects of this study were patients admitted to general SICUs of 9 university-based hospitals aged 18 years and over. Patients who did not benefit from ICU admission were excluded.

Patient data were gathered in 3 main phases: on admission, at discharge, and from daily recordings of data. Admission case record forms (CRFs) were used on admission. Daily CRFs were recorded during ICU stay and patients were followed until discharge from the ICU or up to 28 days after ICU admission. Discharge CRFs were recorded when patients were discharged from the ICU. These patients were followed-up for up to 28 days following discharge from the ICU if they survived. Admission CRF consisted of: 1) Demographic data, 2) Underlying disease(s) and drug usage, 3) ICU admission details, 4) Post operative details, 5) Diagnosis, and 6) Severity of diseases. Daily CRF consisted of: 1) Adverse event surveillance, 2) Vasoactive drug usage in ICU; 3) Monitoring of all catheter(s) and equipment. Discharge CRF consisted of: 1) ICU discharge details, 2) Hospital discharge details, 3) follow-up 28 days after ICU discharge.

All patients in this study provided standard informed consent. The research proposal and all CRF were approved by the Thailand Joint Research Ethics Committees (JREC) as well as each institution's Ethics Committee (EC) or Institutional Review Board (IRB) prior to the collection of any data.

Regarding analysis planning, the statistical program used in this study was STATA, version 11.0 (STATA Inc., College Station, TX). Descriptive data were reported as percentages in categorized data and either mean with standard deviation (SD) for parametric distribution, continuous data or median and interquartile range (IQR) for non-parametric distribution, continuous data. Univariable data was analyzed to compare the differences between groups using a t-test, the Mann-Whitney U test and ANOVA. Continuous variables were analyzed using a Kruskal-Wallis test at their distribution. The Chi-square or Fisher exact probability test was employed for categorical data. Relationships between the predictor and outcome variables were analyzed by regression analysis with univariable or multivariable controls. A mixed model was used for repeated measurement variables and cluster analysis. Statistically significant differences were defined as $p<0.05$.

Results

The study included 9 university-based hospital SICUs comprising 4,652 patients, (Table 1). With respect to vasopressor drug uses, the vasopressor exposed patient group comprised 1,155 patients (24.8%), 682 of whom were male (59%) with an average age of 66 (IQR; 53-76) years, BMI of 22.2 (IQR; 19.6-25.0), APACHE II score of 16 (IQR; 11-23), and SOFA score of 6 (IQR; 3-9). With respect to the inotrope exposed group of 372 patients (8.0%), the average age was 66 (IQR; 54-78) years, 212 patients were male (57.0%), average BMI was 22.5 (IQR; 20.0-25.4), APACHE II score was 13 (IQR; 8-19), and SOFA score 4 (IQR; 2-8.5). One fifth of the patients (907 out of 4,652 patients) manifested sepsis at least once at some point during their SICU stay. The vasopressor exposed group had significantly higher risks of ICU mortality, 28-day mortality and new arrhythmia than the non-vasopressor exposed group ($p<0.001$) while the inotrope exposed group also had significantly higher risks compared with the non-inotrope exposed group ($p<0.001$).

Tables 2 and 3 show details of each vasoactive drug usage and outcomes within the groups who used vasopressors and inotropes. The most frequently used vasopressor was norepinephrine (879/1,155 patients; 76.1%). Dopamine was the second most frequent vasopressor of choice (625/1,155 patients; 54.1%) and epinephrine was the third most frequent drug (190/1,155 patients; 16.5%) used. These vasoactive drugs were individually considered in aspect of the main outcomes. The results show that each vasopressor exposure always induced significantly more unfavorable outcomes. The analysis of inotrope use indicated that there were totally 372 patients exposed to inotropes of which the most frequently used was dobutamine (362/372 patients; 97.3%) while the less frequently used was milrinone (27/372 patients; 7.3%). Treatment with these inotropes usually started on the second day of SICU

Table 1. Baseline characteristics of the surgical intensive care unit (SICU) patients: categorized in context of vasopressor and inotropic therapy

	Vasopressor drug			Inotropic drugs		
	Exposure n = 1,155	Non-exposure n = 3,497	*p*-value	Exposure n = 372	Non-exposure n = 4,280	*p*-value
Characteristics						
Male, n (%)	682 (59.05)	2,047 (58.54)	0.759	212 (56.99)	2,517 (58.81)	0.494
Age, median (IQR)	66 (53-76)	64 (50-75)	0.001	66 (54-78)	64 (51-75)	0.007
BMI, median (IQR)	22.22 (19.57-24.97)	22.31 (19.56-25.33)	0.147	22.49 (20-25.39)	22.22 (19.53-25.15)	0.211
APACHE II score, median (IQR)	16 (11-23)	9 (6-13)	<0.001	13 (8-19)	10 (7-15)	<0.001
SOFA score, median (IQR)	6 (3-9)	2 (0-3)	<0.001	4 (2-8.5)	2 (1-5)	<0.001
Admission diagnosis, n (%)						
Cardiovascular	168 (14.55)	571 (16.33)	<0.001	66 (17.74)	673 (15.72)	0.002
Respiratory	96 (8.31)	265 (7.58)		26 (6.99)	335 (7.83)	
Abdominal (GI-HBP)	418 (36.19)	1,451 (41.49)		161 (43.28)	1,708 (39.91)	
Neuro-head-neck	35 (3.03)	201 (5.75)		10 (2.69)	226 (5.28)	
Sepsis	133 (11.52)	39 (1.12)		27 (7.26)	145 (3.39)	
Trauma	111 (9.61)	216 (6.18)		26 (6.99)	301 (7.03)	
Metabolic	13 (1.13)	69 (1.97)		6 (1.61)	76 (1.78)	
Hematological	1 (0.09)	1 (0.03)		0 (0.00)	2 (0.05)	
Renal-GU	73 (6.32)	300 (8.58)		20 (5.38)	353 (8.25)	
Ob-gyn	13 (1.13)	111 (3.17)		5 (1.34)	119 (2.78)	
Musculo-skeletal-skin	84 (7.27)	226 (6.46)		24 (6.45)	286 (6.68)	
Others	10 (0.87)	47 (1.34)		1 (0.27)	56 (1.31)	
Type of surgery, n (%)						
Emergency	405 (35.06)	743 (21.25)	<0.001	132 (35.48)	1,016 (23.74)	<0.001
Elective	280 (24.24)	2,031 (58.08)		121 (32.53)	2,190 (51.17)	
Not define	28 (2.42)	162 (4.63)		9 (2.42)	181 (4.23)	
Not operation	442 (38.27)	561 (16.04)		110 (29.57)	893 (20.86)	
Underlying disease, n (%)						
Hypertension	552 (47.79)	1,716 (49.07)	0.451	182 (48.92)	2,086 (48.74)	0.945
CAD	112 (9.70)	348 (9.95)	0.802	49 (13.17)	411 (9.60)	0.027
CHF	40 (3.46)	67 (1.92)	0.002	16 (4.30)	91 (2.13)	0.007
Vascular disease	74 (6.41)	194 (5.55)	0.277	30 (8.06)	238 (5.56)	0.047
Previous stroke	73 (6.32)	203 (5.80)	0.520	22 (5.91)	254 (5.93)	0.987
Other cardiovascular	103 (8.92)	268 (7.66)	0.173	37 (9.95)	334 (7.80)	0.143
Asthma	14 (1.21)	61 (1.74)	0.213	6 (1.61)	69 (1.61)	0.999
COPD	61 (5.28)	151 (4.32)	0.173	16 (4.30)	196 (4.58)	0.805
Other respiratory	27 (2.34)	107 (3.06)	0.203	10 (2.69)	124 (2.90)	0.817
DM	266 (23.03)	752 (21.50)	0.277	78 (20.97)	940 (21.96)	0.656
Chronic renal failure	152 (13.16)	290 (8.29)	<0.001	37 (9.95)	405 (9.46)	0.760
HIV positive/AIDS	7 (0.61)	11 (0.31)	0.167	1 (0.27)	17 (0.40)	0.702
Malignancy	200 (17.32)	527 (15.07)	0.068	49 (13.17)	678 (15.84)	0.174
Immune disease	21 (1.82)	35 (1.00)	0.027	2 (0.54)	54 (1.26)	0.219
Organ transplantation	12 (1.04)	13 (0.37)	0.007	4 (1.08)	21 (0.49)	0.139
Unknown	66 (5.71)	158 (4.52)	0.100	27 (7.26)	197 (4.60)	0.022
N/A	265 (22.94)	911 (26.05)	0.035	85 (22.85)	1,091 (25.49)	0.261
Outcomes, n (%)						
ICU mortality	378 (32.73)	69 (1.97)	<0.001	86 (23.12)	361 (8.43)	<0.001
28 day mortality	444 (38.44)	198 (5.66)	<0.001	100 (26.88)	542 (12.66)	<0.001
New arrhythmia	202 (17.49)	24 (0.69)	<0.001	43 (11.56)	183 (4.28)	<0.001

IQR = interquartile range, BMI = body mass index, GI-HBP = gastrointestinal-hepatobiliary and pancreatic, CAD = coronary artery disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus

Table 2. Outcomes of each vasopressor drug use in vasopressor exposed patients

	Dopamine exposure	Non-dopamine vasopressor exposure	*p*-value	Norepinephrine exposure	Non-norepinephrine vasopressor exposure	*p*-value	Epinephrine exposure	Non-epinephrine vasopressor exposure	*p*-value
All cases, n (%)	625 (54.11)	530 (45.89)		879 (76.10)	276 (23.90)		190 (16.45)	965 (83.55)	
First drug (%)	557 (89.12)	-	-	815 (92.72)	-	-	145 (76.32)	-	-
First day (IQR)	1 (1-1)	1 (1-2)	<0.001	1 (1-2)	1 (1-1)	0.037	1 (1-1)	1 (1-2)	0.001
Exposure day (IQR)	2 (1-2)	1 (1-1)	<0.001	1 (1-2)	1 (1-1)	<0.001	2 (2-3)	1 (1-2)	<0.001
New arrhythmia	112 (17.92)	72 (13.58)	0.045	155 (17.63)	29 (10.51)	0.005	41 (21.58)	143 (14.82)	0.020
ICU mortality	232 (37.12)	146 (27.55)	0.001	326 (37.09)	52 (18.84)	<0.001	130 (68.42)	248 (25.70)	<0.001
28 day mortality	267 (42.72)	177 (33.40)	0.001	374 (42.55)	70 (25.36)	<0.001	136 (71.58)	308 (31.92)	<0.001

IQR = interquartile range
Non-dopamine vasopressor exposure: exposure with any vasopressors except dopamine, Non-norepinephrine vasopressor exposure: exposure with any vasopressors except norepinephrine, Non-epinephrine vasopressor exposure: exposure with any vasopressors except epinephrine

admission with dobutamine being applied for a longer period.

The data were analyzed by multivariable analysis (Table 4) adjusting for age, APACHE II score, SOFA score, admission diagnosis, underlying congestive heart failure and chronic kidney disease. In the context of all patients in the study, exposure to each vasopressor significantly increased the risk of unfavorable outcomes but when analyzing in the context of the patients who exposed to vasopressor treatment, it was found that exposure to norepinephrine or epinephrine significantly increased the risk of unfavorable outcomes but dopamine significantly increased only new arrhythmia cases. The adjusted odds ratio of epinephrine in the context of the patients who exposed to vasopressors showed that those on epinephrine had the highest risk of all unfavorable outcomes: OR 3.17 (95% CI 2.10-4.78, $p<0.001$) for ICU mortality, OR 2.62 (95% CI 1.73-3.97, $p<0.001$) for 28-day mortality, and OR 1.77 (95% CI 1.13-2.75, $p=0.012$) for new arrhythmia. With respect to inotropic drugs, multivariable analysis for all patients in the study showed that dobutamine significantly increased all unfavorable outcomes but milrinone showed no significant results. However, an analysis in the context of the patients who were exposed to inotropes, revealed that exposure to dobutamine or milrinone did not demonstrate any significant results.

Discussion

The primary aim of using vasoactive drugs in cardiovascular resuscitation is to optimize tissue perfusion whether by increasing vascular tone or cardiac contractility. In either mechanism of actions, there are many complications related to the use of vasoactive drugs such as cardiac arrhythmia, poor splanchnic perfusion, vasoconstrictor induced poor peripheral perfusion, and stress induced cardiomyopathy[14,15]. The results of the study demonstrated that vasoactive drug use is correlated with unfavorable outcomes. Comparing the groups not exposed to vasopressors or inotropes with those exposed, the exposed groups had significantly higher ICU mortality, 28-day mortality, and new arrhythmia ($p<0.001$ for all outcomes). These outcomes may result from significant differences in patient characteristics.

The authors also analyzed each drug within the groups who used vasopressors and inotropes (Table 2 and 3) to reveal the possible specific effects of each drug aside from primary effects (vasoconstriction or inotropic effect). Norepinephrine was the most

Table 3. Outcomes of each inotropic drug use in inotrope exposed patients

	Dobutamine exposure	Non-dobutamine inotrope exposure	*p*-value	Milrinone exposure	Non-milrinone inotrope exposure	*p*-value
All cases, n (%)	362 (97.31)	10 (2.69)		27 (7.26)	345 (92.74)	
First drug (%)	191 (98.96)	-	-	11 (78.57)	3 (21.43)	-
First day (IQR)	2 (1-3)	2 (1-2)	0.907	2 (1-3)	2 (1-3)	0.966
Exposure day (IQR)	3 (2-7)	1 (1-1)	0.024	1 (1-4)	3.5 (2-9)	0.007
New arrhythmia	48 (13.26)	1 (10.00)	0.764	4 (14.81)	45 (13.04)	0.793
ICU mortality	86 (23.76)	0 (0.00)	0.079	2 (7.41)	84 (24.35)	0.044
28 day mortality	99 (27.35)	1 (10.00)	0.222	3 (11.11)	97 (28.12)	0.055

IQR = interquartile range
Non-dobutamineinotrope exposure: exposure with any inotropes except dobutamine, Non-milrinoneinotrope exposure: exposure with any inotropes except milrinone

Table 4. Multivariable analysis to determine the risk of vasoactive drugs on ICU outcomes

	Adjusted odds ratio (95% confidence interval)			
	All patients	*p*-value	Exposed patients	*p*-value
ICU mortality				
Dopamine	3.22 (2.44-4.25)	<0.001	1.29 (0.95-1.73)	0.100
Norepinephrine	5.52 (4.15-7.34)	<0.001	1.97 (1.33-2.91)	0.001
Epinephrine	5.50 (3.54-8.55)	<0.001	3.17 (2.10-4.78)	<0.001
Dobutamine	2.16 (1.50-3.11)	<0.001	1	-
Milrinone	0.34 (0.04-2.63)	0.299	0.26 (0.05-1.41)	0.118
28 day mortality				
Dopamine	2.35 (1.84-3.00)	<0.001	1.26 (0.95-1.68)	0.114
Norepinephrine	2.95 (2.33-3.73)	<0.001	1.59 (1.11-2.28)	0.011
Epinephrine	3.95 (2.58-6.05)	<0.001	2.62 (1.73-3.97)	<0.001
Dobutamine	1.48 (1.07-2.04)	0.018	1.77 (0.19-16.80)	0.618
Milrinone	0.47 (0.09-2.37)	0.360	0.36 (0.09-1.48)	0.157
New arrhythmias				
Dopamine	3.08 (2.27-4.17)	<0.001	1.44 (1.02-2.02)	0.036
Norepinephrine	4.14 (3.05-5.63)	<0.001	1.74 (1.12-2.70)	0.014
Epinephrine	2.16 (1.36-3.41)	0.001	1.77 (1.13-2.75)	0.012
Dobutamine	1.69 (1.17-2.43)	0.005	0.79 (0.09-6.73)	0.828
Milrinone	2.10 (0.66-6.69)	0.211	1.36 (0.43-4.29)	0.605

Adjusted by age, APACHE II score, SOFA score, admission diagnosis, underlying of congestive heart failure and chronic renal failure

frequently used vasopressor and dobutamine was the most frequently used inotrope in all patients. These results might be influenced by sepsis resuscitation guidelines[1]. The increasing mortality in the dopamine exposed group is consistent with SOAP study outcomes[10] but we are still waiting for more information to draw conclusions on the risks of dopamine use. Epinephrine was usually used as a second line vasopressor according to sepsis resuscitation guidelines. These clinical practices could also have led to the increase of ICU mortality and 28-day mortality when it was decided to use epinephrine for cases of

difficult resuscitation. The use of vasopressors, especially epinephrine, has been reported to be related to cause poor gastric mucosa perfusion[12,16]. The inadequate splanchnic perfusion induced enterocyte damage caused by vasopressor use may be a cause of the increased mortality, but this needs to be proven. However, as shown in Table 1, the most common admission diagnosis in SICU patients was intra-abdominal lesions that might have been the cause of poor splanchnic perfusion per se.

Dobutamine was the most frequently used inotrope in the study (Table 3). Comparison between the dobutamine exposed group versus the non-dobutamine inotrope exposed group revealed no statistically significant differences in outcomes between the two groups. In contrast, comparison between the milrinone exposed group versus the non-milrinone inotrope exposed group demonstrated differences in ICU mortality. However, the favorable outcomes in the group exposed to milrinone should be interpreted with caution because only a small number of patients were exposed to milrinone in the study.

Data on the use of each vasoactive drug were analyzed by multivariable analysis adjusted for confounding factors. Dopamine use significantly increased the risk of new arrhythmia as shown in previous studies but did not significantly increase mortality outcomes when compared within the vasopressor exposed group; whereas norepinephrine use increased all unfavorable outcomes. This result is consistent with the SACiUCI study which reported that norepinephrine administration was an independent risk factor for ICU mortality in patients with septic shock[17]. Epinephrine use was associated with the highest risks of all unfavorable outcomes. Dobutamine was associated with significant risks for all unfavorable outcomes when analyzed within the group of all patients. These outcomes might arise from the fact that patients who needed to start dobutamine treatment usually were suffering myocardial contractile dysfunction which is a severe life-threatening condition. However, when analyzed within the group of inotrope exposed patients, dobutamine did not show any significant outcomes. Multivariate analysis of milrinone use also did not show any significant outcomes.

The authors attempted to minimize the effects of confounding factors by multivariable analysis but it is impossible to take all possible confounding factors into account. The results of the study reveal unfavorable outcomes when using vasoactive drugs, particularly vasopressors, even after adjustment for possible confounding factors. However, in fact, the use of vasoactive drugs in shock resuscitation cannot be avoided so they should be used with caution.

Conclusion

This study demonstrates increasing mortality in surgical critically ill patients treated with use of all types of vasopressor drugs under investigation. Epinephrine exposure was associated with the highest risk of unfavorable outcomes. The use of vasopressors to achieve optimal outcomes needs to be debated in the future, whether it is a matter of the proper use of vasopressors or consideration of the specific properties of each vasopressor or of specific patient conditions affecting outcomes. More information is needed before making decisions about which vasoactive drug is better in any particular situation and to monitor the use of these drugs properly for safe outcomes. However, without any definite information, the authors suggest using all vasoactive drugs with caution.

What is already known on this topic?

In addition to the improper use of vasoactive drugs, each drug may have undesirable effects causing unfavorable outcomes. There are controversial issues in study of clinical outcomes in the application of vasoactive agents and limited information in surgical critically ill patients.

What this study adds?

With respect to vasoactive drug use in surgical critically ill patient, epinephrine has the highest risk of unfavorable outcomes with the second highest risk being for norepinephrine.

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Potential conflicts of interest

None.

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การรักษาด้วยยากระตุ้นหลอดเลือดและหัวใจในผู้ป่วยวิกฤตศัลยกรรม: ผลจากการศึกษา THAI-SICU

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วัตถุประสงค์: การศึกษานี้ต้องการประเมินผลกระทบของการใช้ยากระตุ้นหลอดเลือดและหัวใจต่อการเจ็บป่วยและการเสียชีวิตในผู้ป่วยวิกฤตศัลยกรรม

วัสดุและวิธีการ: ดำเนินการศึกษาแบบสหสถาบันเชิงสังเกตไปข้างหน้าในหอผู้ป่วยวิกฤตศัลยกรรมของโรงพยาบาลโรงเรียนแพทย์เป็นระยะเวลากว่า 22 เดือน ข้อมูลผู้ป่วยจะได้รับการบันทึกโดยแบบบันทึกใน 3 ขั้นตอนหลักคือ ช่วงเข้ารับการรักษา ช่วงติดตามการรักษาในแต่ละวันในหอผู้ป่วยวิกฤตศัลยกรรม และช่วงย้ายออก

ผลการศึกษา: จากหอผู้ป่วยวิกฤตศัลยกรรมทั้ง 9 แห่ง ที่เข้าร่วมการศึกษาประกอบไปด้วยผู้ป่วย 4,652 ราย ในจำนวนนี้มีผู้ป่วยที่ได้รับยาตีบหลอดเลือด 1,155 ราย (24.8%) ผลการศึกษาหลักแสดงให้เห็นว่า กลุ่มที่ได้รับยาตีบหลอดเลือดหรือกลุ่มที่ได้รับยากระตุ้นการบีบตัวของหัวใจ มีความเสี่ยงที่สูงขึ้นอย่างมีนัยสำคัญต่อการเสียชีวิตเพิ่มขึ้นในหอผู้ป่วยวิกฤต เพิ่มอัตราการเสียชีวิตภายใน 28 วัน และเพิ่มการเกิดภาวะหัวใจเต้นผิดจังหวะมากกว่ากลุ่มที่ไม่ได้รับยาประเภทนี้ ($p<0.001$) เมื่อวิเคราะห์ข้อมูลโดยการวิเคราะห์หลายตัวแปร การใช้นอร์อีพิเนฟรินหรืออีพิเนฟรินเพิ่มความเสี่ยงต่อการเกิดผลลัพธ์ไม่พึงปรารถนาทุกอย่างดังกล่าว การใช้อีพิเนฟรินมีความเสี่ยงสูงสุดต่อการเกิดผลลัพธ์ที่ไม่พึงปรารถนาทั้งหมดโดยมี OR 3.17; 95% CI 2.10-4.78 ($p<0.001$) ต่อการเสียชีวิตในหอผู้ป่วยวิกฤต OR 2.62; 95% CI 1.73-3.97 ($p<0.001$) ต่อการเสียชีวิตภายใน 28 วัน และ OR 1.77; 95% CI 1.13-2.75 ($p = 0.012$) สำหรับการเกิดหัวใจเต้นผิดจังหวะ การวิเคราะห์หลายตัวแปรในบริบทของผู้ป่วยที่ได้รับยากระตุ้นการบีบตัวของหัวใจ ไม่พบว่าโดบูทามีนหรือมิลริโนนแสดงให้เห็นผลการรักษาอย่างมีนัยสำคัญใด ๆ

สรุป: ผู้ป่วยที่ได้รับยากระตุ้นหลอดเลือดและหัวใจมีอุบัติการณ์ที่สูงขึ้นอย่างมีนัยสำคัญของการเสียชีวิตในหอผู้ป่วยวิกฤต การเสียชีวิตภายใน 28 วัน และการเกิดหัวใจเต้นผิดจังหวะ กลุ่มที่ได้รับอีพิเนฟรินเป็นกลุ่มที่มีความเสี่ยงสูงสุดต่อการเกิดผลลัพธ์ที่ไม่พึงปรารถนา ข้อมูลเพิ่มเติมจากการศึกษาที่มีการออกแบบที่ดีเป็นสิ่งจำเป็นเพื่อที่จะนำมาตัดสินการปรับใช้งานที่เหมาะสมที่สุดของยาประเภทนี้ในอนาคต