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Comparing the Use of Dopamine and Norepinephrine in Shock Treatment

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Abstract

Background: The vasopressor agents, such as norepinephrine and dopamine have been endorsed as the standard choice for shock treatment. However, there is controversy regarding the use of vasopressor agents for shock treatment. Considering the use of norepinephrine over dopamine, the present study aimed at assessing the reasons for the reduced death rate among the patients who were in shock.

Methods: Three randomized studies comprising of 62 patients were identified in a meta-analysis that made a comparison of the effects of the two agents on patients suffering from gangrenous shock. Based on the inadequacy of data, a controlled and randomized study was conducted to predict the better results after administration of norepinephrine.

Results: The patients treated with dopamine recorded more arrhythmic occasions than those administered with norepinephrine. The results indicated that norepinephrine is a prudent choice in shock treatment. Norepinephrine was also found to increase in the blood pressure after load, which reduces the cardiac output by increasing the myocardial demand of oxygen.

Conclusion: Even though the death rate did not have a major difference between the patients administered with dopamine and those with norepinephrine, the study raised serious concerns regarding the safety of dopamine therapy. This is because when compared with norepinephrine, dopamine led to more arrhythmias and higher death rate of cardiogenic shock patients.

Keywords: Dopamine; Norepinephrine; Shock; Treatment

Abbreviations: SOAP: Sepsis Occurrence in Acutely III Patients

Introduction

Cardiovascular shock refers to a critical condition that occurs when a patient's heart suddenly fails to pump blood as required by the body. This rare but fatal condition is mostly caused by heart attack and is linked to high death rate [1,2]. The fluid administration that forms the firstline of therapeutic strategy does not offer enough stability for the condition of the patient, and the adrenergic agents are regularly needed to correct hypertension [3]. Among the most frequently used agents are dopamine and norepinephrine. Both dopamine and norepinephrine affect the alpha-adrenergic and beta-adrenergic receptors, though to varying degrees. The effects of alpha-adrenergic receptors lead to increased vascular tone. However, it could decrease the cardiac output as well as the regional flow of blood, particularly in cutaneous, renal, and splanchnic beds [4].

On the other hand, beta-adrenergic effects assist in the maintenance of blood flow through inotropic and chronotropic effects as well as increasing splanchnic perfusion. This stimulation from the beta-adrenergic effects can bring out the unwanted consequences, including an increase in the cellular metabolism and immunosuppressive effects [5]. Besides, dopamine arouses dopaminergic receptors, which leads to a uniformly bigger rise in renal and splanchnic perfusion, which can expedite lung edema tenacity. Conversely, the stimulation caused by dopamine could lead to negative immunological effects by modifying hypothalamic-pituitary function, leading to a patent drop of prolactin as well as the level of hormones [6].

Hypothetically, norepinephrine and dopamine have varying effects in the splanchnic, kidney and pituitary axis, though the medical consequences of the implied differences are not certain [7]. Experts have recommended that any of the two compounds may be chosen first and applied as a vasopressor in patients suffering from shock. Studies have indicated that more deaths are associated with the use of dopamine than the use of norepinephrine [1]. Therefore, by considering the use of norepinephrine over dopamine, the present study aimed at assessing the ways leading to reduced death rate among the patients who are in shock.

Material and Methods

Patient's examination

The study was carried outat various centers in Spain, Belgium, and Austria between April 2003 and September 2007. It included patients over 18 years and above who required a vasopressor agent for treating shock. The following inclusion criteria were taken into consideration: (i) Mean pressure of the patient's artery below 70 mm Hg; (ii) A systolic pressurebelow 100 mm Hg in spite of giving enough fluidsto the patient; and (iii) Hypoperfusion tissue symptoms [8].

The patients who had already been administered with either of the agents, such as norepinephrine, dopamine, epinephrine and phenylephrine, for four hours and above within the current shock episode were excluded [9]. Besides, braindead patients and patients with severe arrhythmia including tachycardia and rapid atrial fibrillation were also excluded from the study. The baseline characteristics of the

patients were collected from the records kept in various health centers where the patients had been admitted, with the permission from the doctor on duty.

An irregular heartbeat is known as arrhythmia. Arrhythmia is of three different types. Tachycardia is the condition where the heartbeat's too fast and bradycardia is the condition where the heartbeat's too slow. Fibrillation is the irregular or premature contraction of muscle fibers of the heart. Apart from a stroke that results from improper pumping of the heart, arrhythmia can contribute to heart failure and Alzheimer's disease as well. Norepinephrine is similar to adrenaline. When during certain medical conditions or surgical procedures blood pressure falls drastically, norepinephrine is used to bring blood pressure to normalcy.

Protocol

The researchers completed randomization using permuted blocks of 6 to 10 that were generated using a computer. These blocks were then stratified depending on the ICU used in the study. A five digit number of reference and assignments for treatment were sealed in opaque envelopes. These envelopes were opened by the person preparing the trial drug solutions for dopamine and norepinephrine in syringes in accordance with the local ICU's preferences [8].

Every syringe was labeled according to the number that had been assigned randomly. All the healthcare practitioners including the research personnel and the data collectors were not aware of the core tasks. This test sought ethics committee's approval from every center of participation. Besides, written consent was obtained from the patients or their close relatives [10].

The administered dose was determined by the patient's body weight. Dopamine doses were added or reduced by 2 µg per kilo in a minute while norepinephrine doses were added by 0.02 µg per kilo in a minute. More doses were provided in the cases of emergency. The doctor in charge of every patient determined the target blood pressure [9]. When the sample remained hypotensive even after the administration of the full dose for either of the agents, the researchers added open-labeled norepinephrine. They chose a full dopamine dose of 20 µg for each kg body weight in every minute as the care standard in participating ICUs, in accordance with the recommendations of experts, which was in line with the international guidelines [11].

The agent replacement was done immediately if the patient was in the treatment process using vasopressor at the baseline. If the patient was under the reception of dopamine even after the trial, it could not be terminated and was substituted with norepinephrine fusion with the open label. The use of open-label dopamine was not allowed during the experiment. Vasopressin and epinephrine were administered as saving therapy. In addition, inotropic agents could be administered, if needed, for an increased cardiac output [12].

While weaning patients from these agents, the norepinephrine in the open-label in the administration process was withdrawn, followed by the withdrawal of the drug solution. In cases of hypotension recurrence, the trial drug was first resumed then an open-label norepinephrine solution was added when needed [13].

The study was completed in 28 days. The drug used in the study was reinstituted in the case of necessity in the patients discharged from ICU, though they were admitted again within 28 days after randomization. This provided enough room and time for drug exposure. After 28 days, the physician in charge was left with the vasopressor agent choice [14].

If adverse effects were observed in the course of the treatment after using the experimental drug, the on-duty physician excluded the patient or the sample from the experiment and set to vasopressor therapy (open label). The other forms of treatment remained with the physicians handling the situation.

Termination points

The determination of the mortality rate on the 28th day was considered as the endpoint. The secondary endpoints involved the death rates during the hospital stay, intensive care unit, at six and twelve months. Others included the period for ICU stay and the total number of days that did not need the sustenance of the organ in which the mean arterial pressure was 65 mm Hg. Besides, administration of dobutamine as well as the variable hemodynamic deviations or other agents that are inotropic was also included [15]. The researchers placed adverse events in various categories including arrhythmias. This included ventricular tachycardia, atrial fibrillation or ventricular fibrillation. Other categories included myocardial necrosis, ischemia in appendages or distal limits, skin necrosis and ancillary contaminations [16].

Measured variables

Data was recorded at intervals of six periods for 48 hours, each 8 h of the 3rd, 4th and 5th day as well as once per day on the 6th, 7th, 14th, 21st and 28th day. It included vital signs, cardiac output and hemodynamic variables (which included arterial pressure in systole and diastole, central venous pressure, heart rate as well as pulmonary artery pressure, whenever possible). Similarly, there was a record on the arterial and mixed venous level of blood, cardiac output, vasoactive agent doses and respiratory conditions [17]. Variables on biology, microbiologic data, everyday fluid balance statistics as well as antibiotic therapy were noted every day during the 1st seven days followed by 14th, 21st and 28th days.

Analyzing statistics

Observational studies indicated that the use of dopamine is perhaps linked to higher death rates than the use of norepinephrine. The study by Manouchehri et al. [2] on Sepsis occurrence in acutely III patients (SOAP), which involved 1058 shock patients, indicated that the independent use of dopamine posed a risk for death in the ICU. According to the study, the results indicated a death rate of 43% among dopamine patients and 36% of norepinephrine patients. It was approximated that having 765 patients in every category, the research would have a supremacy of 80% to indicate a 15% relative disparity in the death rate at the 28th day, which is a double-sided alpha leveling at 0.05.

Given that the degree of the effect resulting from studies under observation is likely to mislead, they chose a sequential trial design that has alternatives on both sides; the trial design demanded the performance of the analyses once the first 50 and 100 patients were included [18]. Then, after including every supplementary 100 patients and terminating the trial in respect to these predetermined limits, dopamine dominance over norepinephrine, norepinephrine superiority over dopamine or lack variance between them was analyzed.

According to the research report, a self-determining statistician along with a physician supervised the effectiveness of the analyses on October 2007. The outcome analysis for the first 1600 patients indicated that among the predefined boundaries which had been traversed, the expert advised the stoppage of the trial.

All the statistical analyses were done with regard to the principle of intention-to-treat [19]. An unadjusted chi-square test was employed to analyze the differences in the primary outcome. The results were offered in the form of total and relative dangers and 95% interims of confidence. The study employed the use of Kaplan-Meier curves (Figure 1) in survival

approximation in comparison with the log-rank test use [20]. The study used a regression model called Cox proportional-hazards in the evaluation of potentially confusing factors in the results. Selection of the factors was done if the value of P in univariate analysis was less than 0.20.

The researchers conducted a predetermined subdivision analysis of the main outcome with regard to the kind of shock that is septic, hypovolemic or cardiogenic. They performed a test for the interface, and its effects are offered in a forest plan (Figure 2).

Analysis of the other double endpoints was done using chi-square tests [21]. The variables that are continuous were compared using unpaired t-test of the student or Wilcoxon rank-sum by using SPSS software. All of the values of P were found to be binary with no adjustments for multiple tests. As the investigators and statisticians involved in the study did the final analyses, they were ignorant of the treatment assignments of the patients.

Results

Among the various studies conducted, it can be generalized that the there was a similarity in the baseline characteristics of the
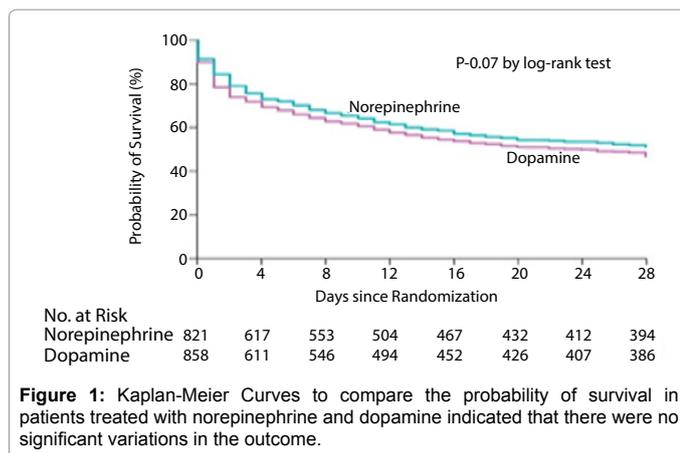
Figure 1: Kaplan-Meier Curves to compare the probability of survival in patients treated with norepinephrine and dopamine indicated that there were no significant variations in the outcome.
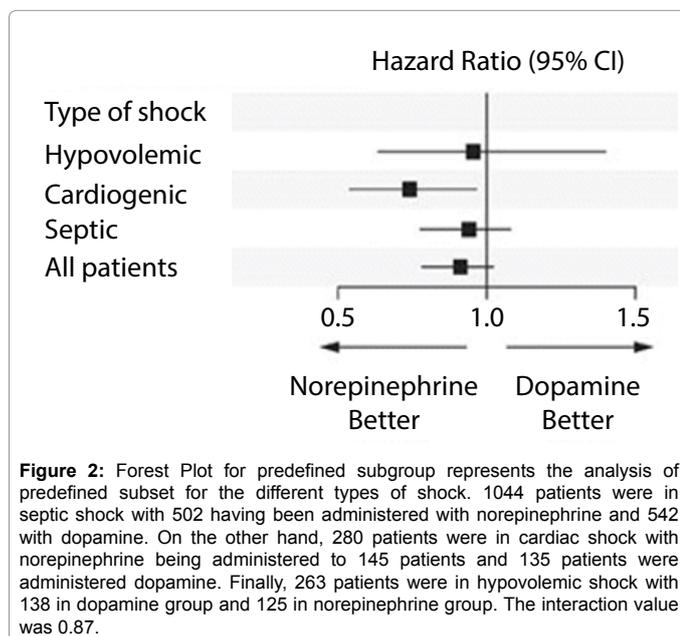

Figure 2: Forest Plot for predefined subgroup represents the analysis of predefined subset for the different types of shock. 1044 patients were in septic shock with 502 having been administered with norepinephrine and 542 with dopamine. On the other hand, 280 patients were in cardiac shock with norepinephrine being administered to 145 patients and 135 patients were administered dopamine. Finally, 263 patients were in hypovolemic shock with 138 in dopamine group and 125 in norepinephrine group. The interaction value was 0.87.

various groups involved. Averagely, no significant difference was observed using either of the agents [22]. However, the patients treated with dopamine recorded more arrhythmic occasions than those administered with norepinephrine as indicated in various (Figure 3 and Table 1), respectively.

Patients

An overall number of 1679 patients were involved, of which 858 belonged to the dopamine group and 821 in the norepinephrine group as shown in Figure 3.

A rise in the heart rate was greatly recorded among the patients who were treated with dopamine compared to the norepinephrine patients [23]. However, there was a similarity in cardiac index changes, oxygen saturation and central pressure in the veins as well as the levels of lactation between the groups.

The differences between the two groups were not that significant with regard to most of the characteristics at the baseline [24].

Outcome

The limit for discontinuing the trial due to inadequate evidence in the disparity between treatments at P-value 0.05 was crossed. There were insignificant differences in death rate between these two groups, especially on the 28th day or the ICU death rates in the hospital at 6 or 12 months as shown in Table 2.

Kaplan-Meier curves used to approximate survival indicated the insignificant differences in the outcomes. The analyses of Cox proportional-hazards (which comprised of the sex, APACHE II score as well as the other pertinent variables) produced similar outcomes [8].

There were more days that did not need trial drug and open-label vasopressors with the norepinephrine group of patients compared to the dopamine group [25]. On the other hand, there were insignificant disparities between the groups that did not need the ICU care and those that did not need organ support [26].

According to De Backer et al. [8], the death rate at 28th day was greater among cardiogenic shock patients who were administered with dopamine than those administered with norepinephrine.

Discussion

Various findings seem to present a strong challenge for the American College of Cardiology and the American Heart Association that provides guidelines recommending the use of dopamine as the standard agent for treating cardiovascular shock [22]. The results indicated norepinephrine to be a more prudent choice [19]. Initial studies indicated that dopamine increases contractility of myocardial tissues allowing the effect of pharmacological titration, and hence, it has been considered and recommended as the first choice for treating shock [27,28].

Further studies have shown that dopamine is preferred and favored as the first line of medication as it increases the arterial pressure mainly through vasoconstriction having little effect on the cardiac output, stroke volume, and the heart rate [29]. Studies carried out have shown that the use of dopamine increases the stroke volume and heart rate. These characteristics thus make it more capable of causing harmful tachyarrhythmias compared to norepinephrine (Table 3) [30].

Different studies have shown comparisons between Norepinephrine and dopamine in different randomized trials and in a less meta-analysis state and came up with a thesis trial showing the relative risk of death

Variable	Dopamine (N=858)	Norepinephrine (N=821)
Age–yr		
Median	68	67
Interquartile range	55-67	56-76
Male sex-no. (%)	507(59.1)	449(54.7)
APACHE II Score†		
Median	20	20
Interquartile range	15-28	14-27
SOFA score‡		
Median	9	9
Interquartile range	7-12	6-12
Reason for admission–no. (%)		
Medical	565(65.9)	532(64.8)
Scheduled surgery	168(19.6)	161(19.6)
Emergency surgery	125(14.6)	128(15.6)
Cause of shock–no. (%)		
Sepsis	542(63.2)	502(61.1)
Lungs	278(32.4)	246(30.0)
Abdomen	138(16.1)	135(16.4)
Urine	51(5.9)	42(5.1)
Catheter	14(1.6)	10(1.2)
Endocardium	9(1.0)	11(1.3)
Mediastinum	10(1.2)	15(1.8)
Soft tissues	11(1.3)	13(1.6)
Other	15(1.7)	20(2.4)
Cardiogenic source		
Myocardial infarction	135(15.7)	145(17.6)
Dilated cardiomyopathy	75(8.7)	86(10.5)
Tamponade	25(2.9)	19(2.3)
Pulmonary embolism	2(0.2)	7(0.9)
Valvular disease	10(1.2)	8(1.0)
After cardiopulmonary bypass	4(0.5)	5(0.6)
Other	19(2.2)	20(2.4)
Hypovolemia	138(16.1)	125(15.2)
Hemorrhage	130(15.2)	116(14.1)
Trauma	17(2.0)	23(2.8)
Gastrointestinal bleeding	31(3.6)	22(2.7)
Bleeding at surgical site	64(7.5)	57(6.9)
Other	18(2.1)	14(1.7)
Dehydration	8(0.9)	9(1.1)
Other	48(5.9)	44(5.0)
Spinal	6(0.7)	8(1.0)
Peridural §	13(1.5)	4(0.5)
Intoxication-related ¶	7(0.8)	4(0.5)
Anaphylactic	3(0.3)	4(0.5)
Miscellaneous	13(1.5)	29(3.5)
Hemodynamic, respiratory, and biologic variables		
Temperature–°C	36.6 ± 1.5	36.6 ± 1.5
Heart rate–beats/min	97 ± 27	95 ± 25|
Mean arterial pressure-mm Hg	58 ± 13	58 ± 13
Mean pulmonary–artery pressure-mm Hg**	27 ± 9	29 ± 8|
Pulmonary-artery occlusion Pressure–mm Hg**	16 ± 6	18 ± 6|
Central venous Pressure–mm Hg† †	13 ± 6	13 ± 5
Cardiac index–L/min/m^2‡ ‡	3.11 ± 1.35	2.77 ± 1.16|
Arterial pH	7.32 ± 0.13	7.32 ± 0.14
$PaCO_2$–mm Hg	42 ± 16	41 ± 14
PaO_2–mm Hg	110 ± 75	123 ± 84§§

Variable	Dopamine (N-858)	Norepinephrine (Ni821)	P Value
Support free days through day 28			
Vasopressors not needed			
Trial drug	11.0 ± 12.1	12.5 ± 12.1	0.01
Open label vassopressors	12.6 ± 12.5	14.2 ± 12.3	0.007
Mechanical ventilation not needed	8.5 ± 11.2	9.5 ± 11.4	0.13
Renal support not needed	12.8 ± 12.4	14.0 ± 12.3	0.07
Intensive care not needed	8.1 ± 10.3	8.5 ± 10.3	0.43
Length of stay-no. of days			
Intensive care unit			0.12
Median	5	5	
Interquartile range	1-11	2-12	
Hospital			0.22
Median	11	12	
Interquartile range	2-28	3-28	
Cause of death in hospital-no			0.31
Refractory shock	196/426(46)	155/381(41)	
Withdrawal or withholding of therapy	193/426(45)	190/381(50)	
Brain death or severe postanoic lesions	37/426(9)	36/381(9)	
Adverse events			
Arrhythmias-no. (%)	207(24.1)	102(12.4)	<0.001
April fibrillation	176(20.5)	90(11.0)	
Ventricular tachycardia	21(2.4)	8(1.0)	
Ventricular stimulation	10(1.2)	4(0.5)	
Myocardial infarction-no. (%)	19(2.2)	25(3.0)	0.29
New infectious episode			
No of episodes			0.69
Median	1	1	
Interquartile range	0-1	0-1	
Patience with at least one episode	674(78.6)	619(75.4)	0.35
Skin ischemia-no. (%)	56(6.5)	34(4.1)	0.09
Mild%	46(5.4)	28(3.4)	
Severe%	10(1.2)	6(0.7)	
Arterial occlusion-no. (%)∫	23(2.7)	20(2.4)	0.12
Areas of figures	5(0.6)	1(0.1)	
Legs	7(0.8)	13(1.6)	
Bowel	11(1.3)	6(0.7)	

± Plus-minus values are means ± SD.
† Mild skin ischemia was defined as a cold and cyanotic skin area, with capillary refill time of more than 2 seconds.
‡ Severe skin ischemia was defined as a cold and black skin, with no bleeding on puncture.
§ Arterial occlusion in an extremity was considered to be present if an extremity was cold, if the capillary refill time was prolonged (>2 s), and if there was no pulse in the nutritive artery. Vascular occlusion in the bowel was considered to be present if bowel ischemia was detected by laparotomy, computed tomography, or colonoscopy.

Table 3: Secondary outcomes and effects.

dobutamine, epinephrine, and norepinephrine are used in the treatment of hypovolemic shock. Severity of shock and its cause is determined by conducting tests on the patient. In normal circumstances, IV fluids are offered besides medications that increase blood pressure.

Conclusion

Observational studies carried out on a smaller scale suggested that dopamine treatment may be detrimental to septic shock patients. On
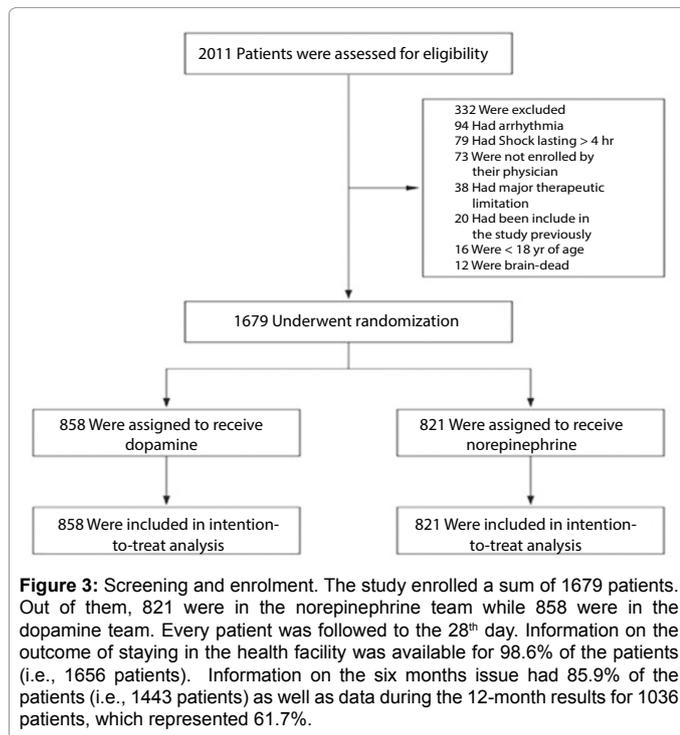
Figure 3: Screening and enrolment. The study enrolled a sum of 1679 patients. Out of them, 821 were in the norepinephrine team while 858 were in the dopamine team. Every patient was followed to the 28th day. Information on the outcome of staying in the health facility was available for 98.6% of the patients (i.e., 1656 patients). Information on the six months issue had 85.9% of the patients (i.e., 1443 patients) as well as data during the 12-month results for 1036 patients, which represented 61.7%.

the contrary, other reports showed higher death rate among the patients who used norepinephrine as compared to dopamine. Even though the death rate did not have a major difference between the patients administered with dopamine and those with norepinephrine, the study raised serious concerns regarding the safety of dopamine therapy. This is because when compared with norepinephrine, dopamine led to more arrhythmias and higher death rate of cardiogenic shock patients.

References

1. Thongprayoon C, Cheungpasitporn W, Harrison A, Carrera P, Srivali N, et al. (2016) Temporal trends in the utilization of vasopressors in intensive care units: an epidemiologic study. BMC Pharmacol Toxicol 17: 19.

2. Manouchehri N, Bigam D, Churchill T, Rayner D, Joynt C, et al. (2013) A comparison of combination dopamine and epinephrine treatment with high-dose dopamine alone in asphyxiated newborn piglets after resuscitation. Pediatr Res 73: 435-442.

3. Dellinger R, Levy M, Rhodes A, Annane D, Gerlach H, et al. (2013) Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. Intensive Care Med 39: 165-228.

4. Finfer S, Vincent J, Vincent J, De Backer D (2013) Circulatory Shock. N Engl J Med 369: 1726-1734.

5. Aletti F, Conti C, Ferrario M, Ribas V, Bollen Pinto B, et al. (2016) ShockOmics: amultiscale approach to the identification of molecular biomarkers in acute heart failure induced by shock. Scand J Trauma Resusc Emerg Med 24: 9.

6. Thiele H, Ohman E, Desch S, Eitel I, de Waha S (2015) Management of cardiogenic shock. Eur Heart J 36: 1223-1230.

7. Mitrić G, Udy A, Bandeshe, H, Clement P, Boots R (2016) Variable use of amiodarone is associated with a greater risk of recurrence of atrial fibrillation in the critically ill. Crit Care 20: 90.

8. De Backer D, Aldecoa C, Njimi H, Vincent J (2012) Dopamine versus norepinephrine in the treatment of septic shock. Crit Care Med 40: 725-730.

9. Nativi-Nicolau J, Selzman CH, Fang JC, Stehlik J (2014) Pharmacologic therapies for anacute cardiogenic shock. Curr Opin Cardiol 29: 250-257.

10. Herrick AL, Murray AK, Ruck A, Rouru J, Moore TL, et al. (2014) A double-blind, randomized, placebo-controlled crossover trial of the 2C-adrenoceptor antagonist ORM-12741 for prevention of cold-induced vasospasm in patients with systemic sclerosis. Rheumatology 53: 948-952.

11. Maas J, Pinsky M, de Wilde R, de Jonge E, Jansen J (2013) Cardiac Output Response to Norepinephrine in Postoperative Cardiac Surgery Patients. Crit Care Med 41: 143-150.

12. Asfar P, Meziani F, Hamel J, Grelon F, Megarbane B, et al. (2014) High versus Low Blood-Pressure Target in Patients with Septic Shock. N Engl J Med 370: 1583-1593.

13. Green JP, Adams J, Panacek EA, Albertson TA (2013) The 2012 Surviving Sepsis Campaign: Management of Severe Sepsis and Septic Shock—An Update on the Guidelines for Initial Therapy. Curr Emerg Hosp Med Rep 1: 154-171.

14. Rock KC, Bakowitz M, McCunn M (2013) Advances in the Management of the Critically Injured Patient in the Operating Room. Anesthesiol Clin 31: 67-83.

15. Radosevich J, Patanwala A, Erstad B (2016) Hepatotoxicity in Obese Versus Nonobese Patients With Acetaminophen Poisoning Who Are Treated With Intravenous N-Acetylcysteine. Am J Ther 23: e714- e719.

16. van der Voort PH, van Zanten M, Bosman RJ, van Stijn I, Wester JP, et al. (2015) Testing a conceptual model on the early opening of the microcirculation in severe sepsis and septic shock. Eur J Anaesthesiol 32: 189-198.

17. Sivayoham N, Rhodes A, Jaiganesh T, van Zyl Smit N, Elkhodhair S, et al. (2012) Outcomes from implementing early goal-directed therapy for severe sepsis and septic shock. Eur J Emerg Med 19: 235-240.

18. Van Zanten A (2014) Guideline bundles adherence and mortality in severe sepsis and septic shock: Results of a National Patient Safety Program in the Netherlands. BMJ Qual Saf 23: 346.

19. Polito A, Parisini E, Ricci Z, Picardo S, Annane D (2012) Vasopressin and terlipressin in adult vasodilatory shock. Crit Care 16: 470.

20. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, et al. (2012) Drotrecogin Alfa (Activated) in Adults with Septic Shock. N Engl J Med 366: 2055-2064.

21. Lian J, Huang X, Pai N, Deng C (2015) Chronic betahistine co-treatment reverses olanzapine's effects on dopamine D2 but not 5-HT2A/2C bindings in rat brains. Prog Neuropsychopharmacol Biol Psychiatry 56:75-80.

22. Zhao JY, Sun JW, Gu ZY, Wang J, Wang EL, et al. (2012) Genetic Polymorphisms of the TYMS Gene Are Not Associated with Congenital Cardiac Septal Defects in a Han Chinese Population. PLoS One 7: e31644.

23. Gordon AC, Mason AJ, Perkins GD, Stotz M, Terblanche M, et al. (2014) The Interaction of Vasopressin and Corticosteroids in Septic Shock. Crit Care Med 42: 1325-1333.

24. Seymour CW, Rosengart MR (2015) Septic Shock. JAMA 314: 708.

25. Radosevich JJ, Patanwala AE, Erstad BL (2015) Norepinephrine Dosing in Patients With Septic Shock. Am J Crit Care 25: 27-32.

26. Verma D, Khuroo T, Talegaonkar S, Iqbal Z (2015) Nanopotentiated combination cancer therapy: Chemotherapeutic and chemosensitizer (2C approach). Med Hypotheses 84: 580-582.

27. Ventura AM, Shieh HH, Bousso A, Góes PF, de Cássia FO, et al. (2015) Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock. Crit Care Med 43: 2292-2302.

28. (2015) Palmer-2C-Läsionen: Arthroskopisches Debridement und sekundäre Ulnaverkürzung. Handchir Scan 4: 201-202.

29. Cheng J, Kozikowski AP (2015) We Need 2C but Not 2B: Developing Serotonin 2C (5-HT 2C) Receptor Agonists for the Treatment of CNS Disorders. Chem Med Chem 10: 1963-1967.

30. Fernández J, Gustot T (2012) Management of bacterial infections in cirrhosis. J Hepatol 56: S1-S12.

31. D'Aragon F, Belley-Cote EP, Meade MO, Lauzier F, Adhikari NK, et al. (2015) Blood Pressure Targets For Vasopressor Therapy. Shock 43: 530-539.

32. Eckert J, Johnson A (1987) Workshop 2C: Advances in diagnosis. Int J Parasitol 17: 1017-1018.