

Nutrition and vasoactive substances in the critically ill patient

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Background

The most common cause of haemodynamic instability (a disturbance of the forces involved in circulating blood through the body) in the critically ill patient is a state of shock, whether it is hypovolaemic, cardiogenic or distributive (septic, anaphylactic or neurogenic) shock.¹ Although the causes of the state of shock differ, the result is the same: decrease in cardiac output and insufficient tissue perfusion;² hence haemodynamic instability. Interventions, including fluid therapy and the administration of vasoactive substances like vasopressors (increase in the vascular tone) and inotropic substances (increase in myocardial contraction) to restore homeostasis (haemodynamic stability), are of critical importance to prevent further deterioration.³

Furthermore, it is well known that the critical care patient benefits from early initiation of nutritional therapy^{4,5} with improved outcomes like reduced length of stay (LOS) and mortality.⁵ However, nutritional therapy must only be started when the patient has been successfully resuscitated and is haemodynamically stable.³ Moreover, the need for vasoactive drugs to maintain haemodynamic stability needs to be considered when initiating nutrition therapy, as these substances can, at high doses, cause feeding intolerance.⁶

During the initial phase of shock,¹ a decrease in blood pressure activates the sympathetic nervous system (the division of the autonomic nervous system that dominates during emergency states),⁷ which mediates the compensatory phase of shock.⁸ In the compensatory phase, to maintain blood flow to the vital organs and to maintain cardiac output, the sympathetic nervous system is activated.^{1,7,8} The effect of stimulation of the adrenergic system is of specific interest because the vasoactive drugs mimic the result of the sympathetic nervous system.⁹ The adrenergic receptors consist of alpha (α) and beta (β) receptors. These can be subdivided into α_1 , α_2 , β_1 and β_2 receptors.¹⁰ The effect of the catecholamines (adrenaline [epinephrine] and noradrenaline [norepinephrine]) on the different organs or tissue depends on which one of the adrenergic receptors dominates in a specific organ or tissue and the nature of the biochemical response that follows.²

The heart is driven by beta receptors.⁸ Stimulation of these receptors causes an increase in heart rate and contractility, improving cardiac output and organ perfusion.⁹ The vasculature bed (network of blood vessels) of non-vital organs, like the splanchnic organs (including the small intestine), consists mainly of α_1 receptors that cause vasoconstriction when stimulated.^{2,9} Therefore, gut ischaemia can ensue in a vasoconstrictive state through inappropriate stimulation with high-volume

enteral feeds.⁵ During stress, both alpha and beta receptors are stimulated, resulting in blood being shunted away from the non-vital organs and towards vital organs.²

The non-vital organ that reacts first to a state of shock is the gastrointestinal (GI) system,¹¹ which experiences decreased blood flow and oxygenation with attendant hypoxia and ischaemia of the villus tip during the compensatory phase and even for a while after blood flow is restored;¹¹ thus, enteral feeds are not optimally tolerated.¹² The start of nutrition, requiring oxygenation and perfusion to accommodate normal digestion in the presence of intestinal ischaemia, puts more stress on the already oxygen-deprived GI system.

To emphasise, it is important to monitor haemodynamic stability in conjunction with vasoactive substance dose. Continuous monitoring of physiological parameters (also known as shock endpoints) signals improvement or worsening in tissue perfusion and oxygenation.⁸ Heart rate, blood pressure and urine output are considered basic endpoints, where a resolution of tachycardia, a mean arterial blood pressure (MAP) of >60–65 mmHg⁴ and a normal urine output may indicate an improvement.^{8,13} In the presence of anaerobic metabolism, increased lactic acid is produced.⁸ If the production of lactic acid exceeds the ability of the liver to excrete excess lactic acid, the serum lactate level will increase.⁸ The stabilisation or decrease⁴ of serum lactate levels will indicate an improvement; a lactate level of <2 mmol/l is considered normal.⁸ The arterial base deficit (calculated from pH, partial pressure of arterial oxygen tension and serum bicarbonate) reflects the use of bicarbonate to buffer acidosis.⁸ A reduction of base deficit reflects the successful restoration of tissue perfusion and oxygenation; a base deficit of –2 to 2 mmol/l is considered normal.⁸

The use of these shock endpoints in isolation is limited by the presence of pre-existing conditions (hypertension, liver or kidney dysfunction) as well as the method of measurement (invasive or non-invasive blood pressure). Therefore, they must be considered in conjunction with each other to reflect the true state of perfusion and oxygenation.⁸

The inotropic drugs and vasopressors most often used are adrenaline, dobutamine, dopamine, noradrenaline and phenylephrine, and will be explained.^{2,3,14}

Adrenaline can be used either to increase myocardial contractility by administering it at lower doses (0.01–0.05 $\mu\text{g}/\text{kg}/\text{min}$), predominantly stimulating β_1 and β_2 receptors, or as a vasoconstrictor by administering it at higher doses, predominantly stimulating α_1 receptors.² At doses higher than 2 $\mu\text{g}/\text{kg}/\text{min}$, it is

a pure alpha agonist (stimulant), resulting only in vasoconstriction, decreasing mesenteric (the membrane that connects the intestines to the abdominal wall) and renal perfusion.²

Dobutamine is a pure beta stimulant.² It balances β_1 and β_2 effects to improve cardiac contractility and coronary artery perfusion.² Although it is mainly used in cardiogenic shock, it is occasionally used in septic shock to improve cardiac function.² At a rate of 5 $\mu\text{g}/\text{kg}/\text{min}$, it improves gastrointestinal perfusion in patients with septic shock.²

Dopamine is the precursor of noradrenaline.² At moderate doses of 5–10 $\mu\text{g}/\text{kg}/\text{min}$, it predominantly acts as a β_1 agonist, improving cardiac contractility.² At higher doses of 10–20 $\mu\text{g}/\text{kg}/\text{min}$, it has mainly α receptor effects, resulting in vasoconstriction.²

Noradrenaline has both β_1 and α_1 stimulating properties; therefore, it can increase cardiac contractility as well as vasculature tone (vasoconstriction).² However, the main effect of noradrenaline is vasoconstriction.¹⁵ The mean dose range of noradrenaline is 0.2–1.3 $\mu\text{g}/\text{kg}/\text{min}$, with a maximum dose of 3.3 $\mu\text{g}/\text{kg}/\text{min}$.²

Phenylephrine is a pure alpha stimulant, increasing vascular tone and vasoconstriction.² The average infusion dose is 40–60 $\mu\text{g}/\text{min}$. Dosages as high as 180 $\mu\text{g}/\text{min}$ may be used.²

In summary, whenever these drugs cause alpha stimulation (in general at higher doses), they cause vasoconstriction, and that have the potential to decrease gastrointestinal circulation. Nutritional therapy is inappropriate at this stage, as it increases the splanchnic oxygen demand, and ischaemia may ensue.^{5,16}

Some clinical practice areas refer to the dose of the inotropic drugs and the vasopressors in millilitres per hour (ml/hr). Despite manufacturers' guidelines, the strength of continuous intravenous solutions may differ between clinical practice areas. Accordingly, the dietitian sometimes needs to convert the ml/hr vasoactive substance to a $\mu\text{g}/\text{kg}/\text{min}$ dose.¹⁷

Therefore, the following information is needed before any further calculations can be made: (i) how much of a given drug was added to the carrier solution, for example, 4 mg of noradrenaline dissolved in 100 ml of 5% dextrose, or 8 mg of noradrenaline dissolved in 100 ml of 5% dextrose; and (ii) whether the volume of the drug was removed from the carrier solution to maintain the total volume, for example,

250 mg dobutamine dissolved in 200 ml 0.9% sodium chloride. To explain further, an ampoule of 250 mg dobutamine consists of 20 ml of fluid; if 20 ml was removed from the carrier solution, the total volume of the solution would stay at 200 ml. If it was not removed before adding the dobutamine, the total solution would be 220 ml (in dobutamine this is more pronounced because an ampoule of 250 mg consists of 20 ml of fluid).

When this information is obtained, ml/hr can be converted to $\mu\text{g}/\text{kg}/\text{min}$.¹⁷ It is important to convert milligrams (mg) to micrograms (μg) first (1 mg = 1 000 μg).

$$(i) \frac{(\text{Total microgram} \times \text{milliliter on flow})}{(\text{Ideal body weight} \times 60 \times \text{total millilitre of carrier solution diluted in})}$$

For example, for 8 mg noradrenaline diluted to a total volume of 100 ml, administered at a rate of 6 ml/hr, the ideal body-weight of the patient is 75 kg.

$$(ii) \frac{(\text{Total microgram} \times \text{milliliter on flow})}{(\text{Ideal body weight} \times 60 \times \text{total millilitre of carrier solution diluted in})} = \frac{(8000 \times 6)}{(75 \times 60 \times 100)} = 0.1 \mu\text{g}/\text{kg}/\text{min}$$

Every ampoule of noradrenaline consists of 4 mg/4 ml. If 8 ml fluid was not removed before adding the 8 mg noradrenaline, the calculation would change as follows:

$$(iii) \frac{(\text{Total microgram} \times \text{milliliter on flow})}{(\text{Ideal body weight} \times 60 \times \text{total millilitre of carrier solution diluted in})} = \frac{(8000 \times 6)}{(75 \times 60 \times 108)} = 0.098 \mu\text{g}/\text{kg}/\text{min}$$

Indeed, vasopressors and inotropic drugs are often used in combination and, for interpretation, it must be converted to a nor-epinephrine-equivalent dose.¹⁸ Enteral/parenteral nutrition strategies can be guided according to vasoactive dosage and tolerance.⁶

Case report

A 76-year-old male patient was admitted to the surgical intensive care unit (ICU) with Fournier's gangrene. Fournier's gangrene is a rare, life-threatening bacterial infection of the scrotum, penis or perineum.¹⁹ He received an emergency surgical procedure to debride the necrotic tissue. Co-morbidities included type 2 diabetes mellitus, hypertension and prostate cancer. His estimated weight on admission was 75 kg, estimated height 174 cm, and he had a normal body mass index (BMI 24.4 kg/m^2);²⁰ previous anthropometry and diet history were unavailable. He was ventilated for the first 10 days in ICU; macronutrient recommendations were implemented (Table 1).

Table 1: Requirements in critical care

Requirements	Acute phase, early period (days 1–2) ⁵	Acute phase, late period (days 3–7) ⁵	Late phase/rehabilitation/chronic phase ⁵
Energy	< 20 kcal/kg/d ²¹	20–25 kcal/kg/d ²²	25–35 kcal/kg/d ²³
Protein	Average below 0.8 g/kg/d ²³	Gradual progression to 1.3 g/kg/d ^{5,23,24}	1.5–2.5 g/kg/d ^{23,24}
Carbohydrates	Not to exceed 5 mg/kg/min ⁵		
Fat	Not to exceed 1.5 g/kg/d ⁵		
Omega-3 (EPA*/DHA [†]) for EN [∞]	1.5–3.5 g/kg/d ⁵		
Omega-3 Fish oil in PN [~]	> 0.1–0.2 g/kg ⁵		
Fibre	10–20 g fermentable soluble fibre in haemodynamic stability ⁴ in a divided dose over 24 hr in the post-acute phase. ^{4,25} Fibre containing formulas should not be used in the acute phase, especially when there is a risk of bowel ischaemia ^{4,25}		
Glutamine	0.2–0.3 g/kg/d; no glutamine in renal and liver failure ⁵		

EPA = eicosapentaenoic acid; [†] DHA = docosahexaenoic acid; [∞] EN = enteral nutrition; [~] PN = parenteral nutrition.

No feeding was commenced on day zero. The dietitian's daily nutrition assessment included monitoring for haemodynamic stability (on the blood gas report, the following basic shock endpoints were monitored: serum lactate, base excess and the MAP on the ICU vital monitor) (Table 2).

Day 1

On day 1, in the ICU (09:00), the patient's MAP was 67 mmHg with a moderate dose adrenaline of 8 ml/hr infusion (0.17 µg/kg/min; 20 mg adrenaline × 1000 × 8 ml/hr / 75 kg × 60 × 200 ml carrier solution) (Table 2). An hour later (10:00), the patient's MAP was 50 mmHg, and adrenaline was increased to 18 ml/hr (0.4 µg/kg/min).

The MAP then started to stabilise (> 65 mmHg) throughout day one, and adrenaline was decreased gradually to 16 ml/hr (0.35 µg/kg/min) and later to 12 ml/hr (0.26 µg/kg/min) (Table 2), the latter being within an acceptable range to start feeding.^{6,26} Subsequently, trophic enteral nutrition (EN) feeds commenced^{5,27} at 5 ml/24 hr, a semi-elemental peptide base feed⁴ (1.3 kcal/ml) via nasogastric tube (NGT).

Day 2

Adrenaline was stable at 10 ml/hr (0.22 µg/kg/min, moderate dosage).^{6,26} Therefore, trophic feeds were increased to 10 ml/hr, to be increased to 15 ml/hr. However, the latter did not happen as the patient was kept nil per os (NPO) for theatre intervention.

Day 3

The patient was unstable at 07:00 (MAP < 65 mmHg), and serum lactate value also increased significantly (Table 2).

Consequently, noradrenaline was also added at 10 ml/hr (0.04 µg/kg/min). Adrenaline was correspondingly increased to 25 ml/hr (0.55 µg/kg/min) in the early morning, which was too high, thus precluding feeding.⁶ Parenteral nutrition (PN) was therefore considered, but it was not initiated because of unstable serum lactate levels.²⁸

Later in the day, the adrenaline was decreased to 20 ml/hr (0.44 µg/kg/min), after that 18 ml/hr (0.4 µg/kg/min), and then it was stabilised on 10 ml/hr (0.22 µg/kg/min) for a few hours. Throughout the day, noradrenaline was kept at 10 ml/hr (0.04 µg/kg/min). Furthermore, with the increasing vasoactive substances, the serum lactate responded and decreased (Table 2).

Day 4

Adrenaline was still stable at 10 ml/hr (0.22 µg/kg/min) with a stabilised MAP (> 65 mmHg). Noradrenaline was gradually decreased from 10 ml/hr (0.04 µg/kg/min) later in the day to 6 ml/hr (0.03 µg/kg/min). Early in the day, the dietitian assessed that the total ongoing vasoactive dosage (0.26 µg/kg/min) was within the acceptable range to initiate feeding.⁶ However, the patient was kept NPO as he needed to return to the theatre for an oozing wound. The option to start PN was again considered, but his serum lactate was still too high.²⁸

Day 5

Adrenaline was stable at 10 ml/hr (0.22 µg/kg/min) during most of the day. It was reduced to 5 ml/hr (0.11 µg/kg/min) at 18:00 and stopped entirely at 19:00 as his MAP stabilised. Noradrenaline was at 10 ml/hr (0.04 µg/kg/min) during most of the day and was decreased to 2 ml/hr (0.01 µg/kg/min). Throughout

Table 2: Shock endpoints and vasopressor dosages for case report

Day in intensive care unit	Lactate (mmol/l)	Base excess (mmol/l)	MAP, ranging from lowest to highest (mmHg)	Inotrope/ vasopressor (type and dosage)			Vasoactive dosage and related risk of feeding intolerance ⁶
				Adrenaline (ml/hr)*	Noradrenaline (ml/hr) [‡]	Norepinephrine equivalent dosage (adrenaline + noradrenaline) (µg/kg/min)	
0	3.2–9.1	–16.0 – –1.7	68–94	6–20	0	0.13–0.44	Moderate to high dosage; significant risk of feeding intolerance
1	2–3	–8.8 – –0.4	50–75	8–20	0	0.17–0.44	Moderate to high dosage, significant risk of feeding intolerance
2	1.7–2.3	0.7–2.6	68–84	5–10	0	0.11–0.22	Moderate dosage – acceptable to feed; however, risk of feeding intolerance
3	1.7–10.8	–9.5–1.6	56–78	10–25	10	0.26–0.6	Moderate to high dosage, significant risk of feeding intolerance
4	1.4–1.9	–2.4–1.6	61–88	4–14	10	0.13–0.36	Moderate dosage – acceptable to feed; however, risk of feeding intolerance
5	1.6–1.7	–2.5–1.7	65–88	5–10	5	0.13–0.24	Moderate dosage – acceptable to feed; however, risk of feeding intolerance
6	0.9–1.4	1.4–6.2	62–98	0	1	0.004	Optimal dosage to feed
7	1.1–1.5	5.9–8.7	81–110	0	0	0	No inotropes/ vasopressors prescribed, continue to monitor for feeding intolerance
8	1.5–1.7	5.7–10.3	79–119	0	0	0	
9	1.3–1.5	11.8–14.9	67–102	0	0	0	

* In this ICU, the adrenaline was mixed as 20 mg adrenaline (20 ampoules) in 200 ml carrier solution; [‡] 4 mg noradrenaline (1 ampoule) in 200 ml carrier solution.

the day, the total dosage of vasoactive substances was on average 0.26 µg/kg/min (moderate dosage; within an acceptable range to feed enterally).⁶ Furthermore, throughout the day serum lactate was between 1.6 and 1.7 mmol/l. It was decided to reintroduce trophic semi-elemental feeds (5 ml/24 hr). Moreover, it was post-day 3 and thus far he had received an inadequate energy intake from EN; the decision was also made to start supplemental parenteral nutrition (SPN) (25 ml/24 hr)^{5,28} (Table 3).

Day 6

Noradrenaline at 1 ml/hr (0.004 µg/kg/min) with a MAP that stayed mostly above 65 mmHg and no change in inotropes/vasopressors was introduced. The semi-elemental feed was increased to 15 ml/24 hr, and the SPN to 35 ml/24 hr (Table 3).

Day 7

Adrenaline and noradrenaline infusions were discontinued on account of a normal MAP (> 65 mmHg) and serum lactate (< 2 mmol/l). Although base excess was high (8.7 mmol/l), all other parameters were normal. The semi-elemental EN was increased from 10 ml to 25 ml/24 hr, and SPN to 45 ml/24 hr (Table 3).

Day 8

The discontinuation of the adrenaline and noradrenaline infusions was maintained. Energy provision was similar to day 7 (24 kcal/kg), while SPN was reduced to 30 ml/hr, and semi-elemental EN was increased to 35 ml/hr (Table 3).

Day 9

Throughout his ICU stay, the patient did not show signs of EN intolerance.^{3–5} The dietitian stopped SPN and increased EN while also changing to a diabetic polymeric feed to run at 73 ml/24 hr; this feed was prescribed until day 15 in ICU.

Days 10–40

Accordingly, the patient was doing well and was discharged to the surgery ward, where he continued with EN (diabetic polymeric feed at 73 ml/24 hr) for an additional two days. After that, the patient's NGT was removed, and he progressed from a diabetic full-liquid diet to a diabetic soft diet while throughout receiving additional diabetic oral nutritional supplements of high energy and protein content. The patient had a 40-day stay in the ward; on hospital discharge, his weight was 67 kg (an estimated 10.7% weight loss, classified as severe malnutrition);²⁹ post-discharge nutrition follow-up was arranged.

Discussion

In cases of sepsis and resulting high dosages of inotropes and vasopressors, feeding should commence slowly with trophic feeding (defined as 10–20 kcal/hr or up to 500 kcal/day) for the initial phase of sepsis, advancing as tolerated after 24–48 hr over a period of a week.⁴ Early enteral nutrition (EEN) was associated with a reduction in 28-day mortality in ventilated adults treated with low (< 0.1 µg/kg/min) or moderate (0.1–0.3 µg/kg/min) dose vasopressors, but not in the case of high-dose (> 0.3–0.5 µg/kg/min) vasopressors.²⁶

It should always be borne in mind that, as reported in the case study for days zero to five, the MAP can be above > 60 mmHg⁴ due to high vasoactive substances in unstable states; a false impression can be created that it is safe to feed high volumes of EEN, which is not advised. Indeed, in these situations, caution is needed when feeding due to hypoperfusion of the

Table 3: Feeding regime

Day	Feeding (ml/hr, administration rate of nutrition support)		Energy (kJ)/kcal/kg		Protein (g)		Carbohydrates (g)		Lipids (g)		Omega-3 (g) EN: EPA*/DHA* PN~ Fish oil		Glutamine (g)		Fibre (g)	
	EN [∞]	SPN [#]	EN	SPN	EN	SPN	EN	SPN	EN	SPN	EN	SPN	EN	SPN	EN	SPN
5	5	25	672	2 318	8.94	31.7	21.96	47	4.44	23.6	0.072	3.5	0	4.7	0	0
Total day 5	30		2 990 (9.5 kcal/kg)		39.11 (0.5 g/kg)		68.95		28.04		3.572		4.7		0	0
6	15	35	2 016	3 245	24.12	44.3	65.88	66.1	13.32	33	0.22	5	0	6.6	0	0
Total day 6	50		5 261 (16.7 kcal/kg)		68.42 (0.9 g/kg)		131.98		46.32		5.22		6.6		0	0
7	25	45	3 360	4 172	40.2	57	110	85	22.2	42.5	0.36	6.4	0	8.5	0	0
Total day 7	70		7 532 (24 kcal/kg)		97.2 (1.3 g/kg)		195		65.7		6.76		8.5		0	0
8	35	30	4 692	2 781	56.28	38	153.72	56.6	31.08	28.33	0.50	4.3	0	5.7	0	0
Total day 8	65		7 473 (23.72 kcal/kg)		94.3 (1.26 g/kg)		210.32		59.33		4.8		5.7		0	0
9	73	0	11 038	0	131.4	0	229.5	0	122.64	0	4	0	0	0	40	0
Total day 9	73		11 038 (35 kcal/kg)		131.4 (1.75 g/kg)		229.5 (3 g/kg)		122.64 (1.63 g/kg)		4		0		40	0

[∞]EN = enteral nutrition; [#] SPN = supplemental parenteral nutrition; ~ PN = parenteral nutrition; * EPA = eicosapentaenoic acid; * DHA = docosahexaenoic acid.

gastrointestinal tract.⁶ Conversely, Belletti *et al.*³⁰ reported that continuous adrenaline infusion in critically ill candidates is not to be considered negative as it does not lead to adverse complications.³⁰ Therefore, value derangements must be communicated frequently within the interdisciplinary team, especially major changes in the MAP, vasopressor and/or inotrope dosages, and serum lactate.⁶ It is also important to monitor a patient's tolerance to EEN^{3,6} (Table 2).

To explain further, on day one the vasoactive dosage was higher than the recommended acceptable dosage value of 0.1–0.3 µg/kg/min,⁶ increasing the risk of feeding intolerance. Moreover, it was also higher than the median of 0.14 µg/kg/min (range 0.07–0.25 µg/kg/min), where more patients were likely to tolerate EN as reported in a New York study with 120 participants.¹⁸ Therefore, no feeding (EN or PN) was commenced.

Furthermore, on day three, noradrenaline at 10 ml/hr (0.04 µg/kg/min), was a low dose on its own, but together with the adrenaline dose of 0.55 µg/kg/min, it added up to 0.59 µg/kg/min, which is > 0.5 µg/kg/min, indicating a significant risk of feeding intolerance related to bowel ischaemia.^{3,6,26} A rising serum lactate of > 2 mmol/l is a sign of instability and usually results in enteral feeding intolerance.^{18,27} In this regard, Merchan *et al.*¹⁸ reported that serum lactate above 2 mmol/l usually resulted in a population receiving a median norepinephrine-equivalent dose of 0.37 µg/kg/min,¹⁸ which could be acceptable for feeding in the presence of appropriate monitoring.⁶

In terms of monitoring, it is imperative to monitor the patient for signs of malabsorption (abdominal distention, increasing nasogastric [NG] tube output, or gastric residual volume [GRV], which is an indication of possible intestinal ischaemia.³ In such cases, ESPEN recommends that enteral feeding should be delayed only when GRV is > 500 ml/6 h⁵; there is decreased passage of stool and flatus; hypoactive bowel sounds [in relation to possible bowel ischaemia];⁵ otherwise in stable patients EEN should be gradually introduced regardless of the presence or absence of bowel sounds;⁵ increasing metabolic acidosis and/or base deficit;⁴ vomiting; and impossibility of reaching more than 20% of energy needs³). Malabsorption poses a risk of aspiration pneumonia, increased length of stay in the critical care unit and increased mortality.³

Conclusion

Early enteral nutrition, albeit trophic feeding, was initiated successfully when vasoactive drugs were administered at a moderate dosage (0.1–0.3 µg/kg/min)^{6,26} while the patient was monitored for gastrointestinal intolerance throughout. SPN had to be prescribed as an interim measure till GI function was restored.

Therefore, in collaboration with the interdisciplinary team, the dietitian must constantly monitor and evaluate feeding tolerance and adjust the feeding regimen in relation to vasoactive substance doses and clinical presentation.

Disclosure statement – No potential conflict of interest was reported by the authors.

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Received: 10-11-2022 Accepted: 10-11-2022