

Revijalni članak

**KONCEPT INFUZIONOG
RASTVORA KAO LEKA
(Infuzioni rastvor je lek)**

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Review article

**CONCEPT ON FLUID
AS THE MEDICATION
(fluid therapy as the medication)**

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Abstract

Fluid prescription is the basis of critical care, emergency and hospital department therapy. Fluid management is directed according to daily fluid needs and output, body weight, sodium, potassium and glucose content. The consideration of potential risks of fluid overload presents advanced strategy in practice. Monitoring and recording of intravenous and other fluid management is of utmost importance but it is usually poor. Scientific research in the last fifteen years announces a new era in fluid therapy. At the beginning, volume of fluid was pointed out both in the area of initial critical care presentation and the period after the resuscitation. Then, the scientific data about fluid composition increased attention to potential adverse effects of fluid and electrolyte accumulation. Finally, it becomes apparent that fluid and electrolyte overload may influence patient outcomes. Everything previously mentioned was mainly studied in critical care patients and produced new apprehension of the fluid as the solitary drug. The aim of this mini review was to point out the importance of defining fluid as the drug and to present main definitions in this area in this moment.

Key words: patient safety; critical incident;
medical errors

Introduction

Fluid therapy has become an area of increasing interest and an emerging paradigm within the emergency and critical care medicine. Scientific data collected over the last 15 years implies that fluid therapy is not composed of simply using fluids for stabilizing and dissolving medications, but it also includes considering indication, type of fluid, dose, duration, de-escalation point and side effects. Changing outcome in critical care patients, in case of fluid overload and in case of using different types of fluid in different clinical scenarios, emphasizes that this scientific area has huge importance.

Indication area

There are 4 types of fluid, according to indication area¹: resuscitation fluids, maintenance fluids, replacement fluids and medical nutrition therapy.

Resuscitation fluid means that fluid therapy is used to stabilize tissue hypoperfusion. According to new Surviving Sepsis Guidelines for septic patients, it should comprise minimum 30ml/kg (ideal body weight) of intravenous (IV) crystalloids in initial fluid resuscitation². In the study of Regemortel et al³, resuscitation fluid is given by rate above 166ml/h.

Maintenance fluid is the provision of fluids to patients whose needs can not be met by means of oral administration⁴. The average amount should

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be about 1-2ml/kg/h, or 25ml/kg. These fluids are given for the purpose of covering daily needs for glucose, water, sodium and potassium. Daily needs for water are about 1ml/kg/h, for glucose 1-1.5g/kg/day (to limit ketosis), sodium and potassium about 1mmol/kg/day.

Replacement fluids are fluids and electrolytes administered when losses can not be corrected orally or enterally.

Medical nutrition therapy consists of parenteral, enteral nutrition and oral supplements containing water as a part of composition. Various enteral formulas contain around 80% of water. This volume is frequently not included in the calculation of daily fluid balance.

Drug selection

Two important scientific areas of resuscitation fluid in the last decade have been the choice between colloids vs crystalloids and the choice among crystalloids, balanced or unbalanced fluids. Critical and emergency care studies analyzed different outcomes of patients resuscitated with colloid or crystalloid fluids^{5,6}. The studies included a significant number of patients from different parts of the world and were conducted in single or a multicenter intensive care units (ICU)⁷. Some of the studies showed increased risk of renal replacement therapy and increased risk of death if colloids were used as resuscitation fluids^{6,8,9}. On the other hand, Annane et al¹⁰ revealed no difference in mortality, fewer deaths and more days alive on mechanical ventilation in colloid group. However, when comparing starches with crystalloids, based on data obtained from different studies^{6,7,10,11,12}, the European Medicine Agency Pharmacovigilance Risk Assessment Committee concluded, in 2013, that “the benefits of solutions containing hydroxyethyl starches no longer outweigh their risks” and therefore recommended “that the marketing authorizations for these medicines be suspended¹³”.

Relying on previous data, the guidelines on patients with sepsis², trauma¹⁴ and burns¹⁵ emphasized the importance of using crystalloids as resuscitation fluids. The second area of investigation related with fluid-medication selection enclosed studies on different outcomes in critical patients when using unbalanced versus balanced

crystalloids. The definition of balanced fluids has its origin in studies which compare different tonicity of fluids and more importantly, fluids with different chloride content. Namely, Wilcox et al¹⁶ measured glomerular filtration rate (GFR) during the acute increase of sodium, chloride or osmolality in denervated greyhounds' kidneys. The infusion of increased tonicity solutions produced renal vasodilatation with the increase in GFR. In contrast, during the infusion of chloride solutions, vasodilatation was reversed after 1-5min and both renal blood flow and GFR decreased below pre-infusion level. The authors concluded that hyperchloremia produces progressive renal vasoconstriction and decrease in GFR that is independent of the renal nerves. Study of Chowdry et al¹⁷ on healthy volunteers showed that infusion of 0.9% saline resulted in the reduction of renal blood velocity and renal cortex perfusion. The impact of a fluid composition of chloride ion on the outcome, once again emphasized the importance of fluid composition (Table 1).

The implementation of chloride-restrictive strategy in ICU hemodynamic resuscitation protocol during clinical study of Yunos et al¹⁸ showed incidence of reduced acute kidney injury and renal replacement therapy after implementation. Semler et al¹⁹ performed investigation in five ICU's on more than 15,000 patients and compared the outcomes when 0.9% NaCl or Plasma-Lyte and Lactated Ringer's solution were used. They found small difference in major kidney adverse events within 30 days. Based on the data presented above, it can be stated that balanced crystalloids, with low chloride content, are gradually being used as the drug of choice for hemodynamic resuscitation in the majority of critical care settings.

Criteria for medication selection

Crystalloid formulations vary widely between different countries. There is a lack of chemical composition information on the products. Misunderstanding of osmolality and osmolarity is present and should be clearly defined²⁰. Osmolality presents number of osmotically active particles (osmoles) per kilogram of water. It can be measured, or it is calculated from theoretical osmolarity with correction factor²¹.

Theoretical osmolarity is calculated using different formulas and different common osmotically active particles. Previously there were formulas

calculating glucose, urea and sodium. Now, there are several formulas with more precise calculations and more active osmoles taken into account²¹.

Tonicity is effective osmolality and describes the distribution of the fluid thorough the body.

Summarized data important for everyday fluid prescription including osmolality, osmolarity and tonicity are presented in the Table 1.

Medication dosage

If we take into account several different indications for fluid treatment, we should define the medication dosage. Namely, the initial volume, infusion speed and daily amount of specific type of fluid should be valorized for each indication. This evolving scientific area is characterized with variety of different monitoring solutions.

Table 1. Fluid composition and characteristics.

Parameter (mmol/L)	Plasma	0.9%NaCl	Hartman solution	5% Glucose
Na	135-145	154	131	/
K	3.5-4.5	/	5	/
Ca	2.2-2.6	/	2	/
Cl	94-111	154	112	/
Mg	0.8-1.1	/	/	/
Lactate	1-2	/	28	/
Bicarbonate	22-26	/		/
Glucose (g/L)	0.45-0.95	/	/	50
Osmolality (mosmol kg ⁻¹ H ₂ O ⁻¹)	288	286	256	290
Theoretical osmolarity (mosmol L ⁻¹)	291	308	276	278
Tonicity	/	isotonic	isotonic	hypotonic

In this way, fluid bolus is rapid infusion for the correction of hypotensive state. Therefore, it is primarily used as therapeutic option. We use fluid challenge about 4ml/kg of fluid over 15min with the aim of gradually increasing circulatory filling pressure and distinguishing between responders and non-responders²². Therefore, it has primary diagnostic application.

Daily fluid balance is the daily difference between fluid input and output. Fluid balance can be calculated by subtracting urine, gastrointestinal and drainage output from the sum of all daily fluid inputs (intravenous, enteral fluid administration and blood products).

Cumulative fluid balance is the sum of fluid accumulation or positive daily fluid balance, over a period of time. It can be calculated during different periods of time. Positive cumulative balance

is associated with increased intraabdominal pressure²³ and increased risk of renal failure²⁴ and poor outcome²⁵ in critical care patients.

Fluid accumulation is calculated using the following formula:

Fluid overload is defined as a 10% increase in admission weight and/or developing of oedema, crackles, anasarca^{26,27,28}. It is associated with an increased risk of mortality, prolonged hospitalization and changed outcome of critical care patients²⁹. According to study of Kelm et al²⁷ fluid related medical interventions (thoracocentesis, diuretics) are related to fluid overload.

Duration and de-escalation

Fluid therapy as a treatment has a duration, same as any other medication. One of the

consequences of fluid overload is interstitial fluid accumulation, which was experimentally studied by Guyton³⁰, more than 50 years ago. Overzealous fluid resuscitation with positive fluid balance and elevated central venous pressure are risk factors for increased complications rate, increased length of ICU stays and higher mortality³¹. Cordemans et al²⁵ emphasized that increased capillary leak index, extravascular water index and fluid balance are all associated with poor 28-day outcome. These authors suggested treatment pathway named PAL concept with the aim of achieving deresuscitation that should facilitate fluid elimination after initial resuscitation. In this way, Late Goal Directed Fluid Removal was introduced as a new idea in the critical care setting. In the systematic review³², late conservative fluid management was defined as two consecutive days of negative fluid balance in the first 7 days of ICU stay. This concept has been shown as an independent predictor of survival in ICU.

The idea of fluid overload repercussion on outcome, evolves further into different phases of critically ill patient treatment. Conceptual model of Hoste et al³³ and ROSE model of Malbrain et al³² pointed out different phases of fluid treatment course in the critical care patients. These phases are resuscitation phase, optimization phase, stabilization phase and escalation phase. These phases are neatly connected with the patient's course of illness. Recognizing each phase of fluid treatment course sets limits concerning the dose of the fluid.

Resuscitation phase

Early goal directed fluid therapy that was suggested by Surviving sepsis campaign² is one treatment guideline of hemodynamic resuscitation. Another proposed treatment protocol is rapid bolus of 3-4ml/kg fluid given over 10-15 minutes in a repeated manner, if needed. Hemodynamic resuscitation should be considered together with the assumption of the loss of endothelial fluid barrier in the specific critical care state³⁴. Furthermore, it should be emphasized that Hippensteel et al³⁵ showed correlation between the amount of fluid given and the range of glycocalyx degradation and edema formation. On the other hand, avoidance

of adequate fluid administration can lead to organ and system dysfunction.

In this way, accurate tapering of fluid dose in this phase is of utmost importance. Different monitoring methods are proposed. A simplified model of relevant monitoring can be achieved through monitoring preload and monitoring fluid response.

Preload monitoring is usually used to set primary information of the fluid status in a specific situation. Central venous pressure monitoring, mean arterial pressure, urine output and volumetric preload parameters like global end-diastolic volume index are frequently used.

Monitoring fluid response is the method used to differentiate patients, namely, to differentiate responders from non-responders²². It is usually done by means of measuring pulse pressure variation, stroke volume variation and passive leg raising. These parameters are important in the setting of the upper limit of fluid treatment in specific patients and specific moments. It presents the excellence in the area of prescribing dose of fluid and the area of technical innovation and raising paradigm. Fluid balance is positive in this phase.

Optimization phase

The optimization phase can be defined as the phase of compensated shock where the main aim is to limit consequences. Monitoring of fluid balance continues from the previous phase and usually includes data from different measuring parameters, such as central venous pressure, invasive arterial monitoring, mixed venous saturation, ultrasound diagnostics and others. According to Malbrain et al³⁶, these parameters have to be combined with perfusion parameters (lactate, capillary refill time) to avoid potential difference in macrocirculation and microcirculation. In this phase, additional fluid should be given cautiously because decompensation is still highly possible.

Stabilization phase

The stabilization phase is a phase where a patient is no longer in the shock state. Replacement fluid therapy and maintenance therapy are indicated. Late conservative fluid management is the objective of this phase of the fluid treatment course.

Zero fluid balance or slightly negative balance are suggested³².

Evacuation phase

The evacuation phase is DE resuscitation phase where fluid removal is potentiated. Frequently, there is an increased spontaneous patient diuresis. Treatment methods are still being studied; however, diuretics, ultrafiltration and physical therapy are currently the ones used. Negative fluid balance is suggested.

ROSE concept of Malbrain and al³² encircle idea of fluid as the drug in the model of the 4D's meaning Drug-Dose-Duration-De-escalation. The authors even further emphasized the idea on the in the new model of fluid stewardship named 7D's: Definitions-Diagnosis- Drug-Dose-Duration-De-escalation-Discharge. In this model meaning of Ds is defined as³⁷:

Definitions (D1) comprise definition of fluid balance, fluid overload, Early adequate fluid management, Late conservative fluid management, Late Goal directed fluid removal.

Diagnosis (D2) meaning defining the problem as hypovolemia or hypervolemia.

Drug (D3) meaning all about fluid as the drug (when to start and stop, when to start and stop removal)

Dose (D4) as to Malbrain group²⁸ the dose determines when the drug becomes poison.

Duration (D5) according to authors³⁶ defined as to stop the fluids when they are not needed and start oral fluid intake.

De-escalation (D6) where fluid is removed and maintained to prevent hypoperfusion.

Discharge (D7) meaning the last step in fluid stewardship which enclose interventions, prevention of adverse reactions and cost reduction.

Side effects

There is potentiated importance of side effects of increased volume of fluid therapy, but also sodium and chloride overload. According to Regemortel et al³, at least quarter of total administration of fluid volume at first 4 days after ICU admission comprises "fluid creep". The authors define "fluid creep" as:

- Fluid added as a vehicle for intravenous and enteral drugs.
- Fluid to which concentrated electrolytes are added for correction of electrolyte disorders
- Fluid (saline and 5% Glucose) that is added in small fluid volumes to keep the lines open.

In the study from 2021. the authors³⁸ emphasized that there is also problem of sodium overload.

Table 2. Examples of sodium load in anti-infective therapy. The data presented in the table are transferred from the summaries of product characteristics presented by Medicines and Medical devices Agency of Serbia <https://www.alims.gov.rs/eng/>

Drug/dose	Amount of sodium per dose mg/mmol	Antimicrobial therapeutic modality	Daily sodium administration with antimicrobial treatment modality (mmol)
Meropenem 1g	208/4	1g/8h	12
Imipenem/Cilastatin 0.5g	37.6/1.6	0.5g /6h	6.4
Piperacilin/ Tazobactam 4g plus 0.5g	261/11.3	4.5g/8h	34
Metronidazol 0.5g	311/13.5	0.5g/8h	40.5
Kolistimetat natrijum 1x10 ⁶ i.j.	23/1	3x10 ⁶ /8h	6
Ceftazidim 1g	52/2.3	2g/8h	13.8

According to authors, “sodium creep” is present combined with fluid overload, but it can exist solitary also. The main origin of increased sodium load is nested in maintenance fluid. Still, there is important burden of sodium loading during pharmacological prescription of different drugs. Important example of the previous is antimicrobial prescription and administration (Table 2).

According to the small prospective observational study of Bihari et al.³⁹ there is association between positive cumulative sodium balance and increased length of mechanical ventilation.

Conclusion

Fluid management is one of the most sophisticated and most important issues in critically ill patients. The approach to fluid therapy has to be individualized in accordance with the patient, the disease and the actual state. New studies on changing comprehension of endothelial function and glycocalyx imply further changes and frequent update in this scientific area.

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