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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Comparison of Transcutaneous and Arterial Blood Gas Analysis in Patients with Sepsis and Septic Shock

Sepsisli ve Septik Şoklu Hastalarda Transkütanöz ve Arter Kan Gazı Analizlerinin Karşılaştırılması

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ABSTRACT *Objective:* To compare the effectiveness of noninvasive pressure of transcutaneous CO_2 ($PtcCO_2$) and O_2 ($PtcO_2$) analyzers with that of conventional blood gas sampling methods in patients with sepsis and septic shock.
Materials and Methods: Patients with sepsis who did not need inotrope support were prospectively assigned to Group I (n = 50). Patients with septic shock who needed inotropes were assigned to Group II (n = 50). Demographic data, laboratory tests, APACHE II and SOFA scores, standard monitoring data, data of blood gas analysis (pH, $PaCO_2$, PaO_2, and SaO_2), and transcutaneous CO_2 and O_2 were collected at the 1st, 2nd, 3rd, and 4th hours.
Results: There was no significant difference between the groups in terms of demographic parameters, baseline WBC, hematocrit, baseline heart rate, CVP, respiratory rate, or PEEP values. Serum urea and creatinine levels were significantly higher in Group II compared to those in Group I; however, albumin levels and MAP were lower in Group II compared to those in Group I. Furthermore, the APACHE II and SOFA scores, PIP, and FiO_2 were significantly lower in Group I.
There was no significant difference between the $PtcCO_2$ and $PaCO_2$ values in Group I. The $PtcCO_2$ values of Group II were significantly lower when compared to those of Group I.
The $PtcO_2$ vs PaO_2 values were significantly lower in Group I. The $PtcO_2$ vs PaO_2 values were significantly lower in Group II. There was a strong correlation between the arterial and transcutaneous CO_2 and O_2 levels in both the groups.
Conclusion: The assessment of $PtcCO_2$ may be an alternative blood gas analysis method in patients with sepsis but not septic shock. Furthermore, $PtcO_2$ measurement may not be a reliable method for patients with both sepsis and septic shock.
Keywords: Sepsis, septic shock, ICU, transcutaneous CO_2, transcutaneous O_2, arterial blood gas analysis

ÖZ *Amaç:* Sepsisli ve septik şoklu hastalarda non-invaziv transkütanöz parsiyel CO_2 ve O_2 basıncı analizörlerininin etkinliğini geleneksel kan arter kan gazı analizi ile karşılaştırmayı amaçladık.
Gereç ve Yöntem: Sepsis-3 tanı kriterlerine göre 'sepsis' tanısı alan hastalar Grup I'e, 'septik şok' tanısı alan hastalar Grup II'ye ayrıldı. Demografik veriler, laboratuar testleri, APACHE II ve SOFA skorları, 1. 2. 3. ve 4. saatlerdeki standart monitorizasyon verileri, kan gazı analizi verileri (pH, $PaCO_2$, PaO_2, SaO_2) ve transkütanöz CO_2 ve O_2 değerleri kaydedildi.
Bulgular: Gruplar arasında demografik parametreler, başlangıç beyaz küre, hematokrit, kalp hızı, CVP, solunum sayısı ve PEEP değerleri açısından anlamlı bir fark bulunamadı. Grup II'de serum üre ve kreatinin seviyeleri belirgin olarak yüksekken, albümin seviyeleri, OAB daha düşüktü. APACHE II ve SOFA skorları, PIP ve FiO_2 Grup I'de belirgin olarak düşüktü.
Grup I'de $PtcCO_2$ ve $PaCO_2$ değerleri açısından belirgin bir fark bulunamadı. Grup II'deki $PtcCO_2$ değerleri $PaCO_2$ ile karşılaştırıldığında belirgin olarak düşüktü. Grup I'de PaO_2 değerleri ile karşılaştırıldığında $PtcO_2$ belirgin olarak düşüktü. Grup II'de PaO_2 ile karşılaştırıldığında $PtcO_2$ değerleri belirgin olarak düşüktü. Her iki grupta da arter ve transkütanöz CO_2 ve O_2 değerleri arasında güçlü bir korelasyon mevcuttu.
Sonuç: $PtcCO_2$ 'nin değerlendirilmesi septik şoklu hastalarda olmasa da sepsili hastalarda alternatif bir yöntem olabilir. $PtcO_2$ ölçümleri her iki gruptaki hastalarda da güvenilir bir yöntem olarak görülmemiştir.
Anahtar Kelimeler: Sepsis, septik şok, YBÜ, transkütanöz CO_2, transkütanöz O_2, arter kan gazı analizi

Introduction

Sepsis is one of the leading causes of mortality and morbidity and has great clinical importance in general intensive care units (ICU) in adults. Microcirculatory perfusion fails due to various mechanisms related to sepsis, which impairs measurement and assessment of peripheral oxygen saturation (SpO_2). Analysis of arterial blood samples is known as 'gold standard' method to evaluate systemic oxygenation in septic patients (1,2).

However, the method used in routine clinical practice is invasive, expensive, painful and time-consuming. Manufacturers are also willing to introduce advanced non-invasive oxygenation monitoring devices and techniques. Nevertheless, the accuracies of these novel devices in different clinical situations are debated and have not been extensively studied.

To our knowledge this is one of the pioneering prospective studies in the literature comparing the transcutaneous O_2 and CO_2 analysis versus arterial blood gas analysis in septic patients in ICU. The aim of the study is to compare the effectiveness of non-invasive transcutaneous pressure of CO_2 ($PtcCO_2$) and O_2 ($PtcO_2$) analyzers versus conventional blood gas sampling in patients with sepsis and septic shock.

Material and Methods

Approval of the study has been obtained from the ethical committee of the faculty (Approval no: 249). A hundred patients, who have been admitted to the ICU with a diagnosis of sepsis or septic shock, were enrolled to the study. All the patients and/or their relatives were informed verbally and also written consent were obtained.

Patients, who are under 18 years old or have body mass indices (BMI) >35 or <18 kg/m^2, were excluded from the study. Patients diagnosed with sepsis were divided into two study groups. Sepsis patients without a need for inotrope support (sepsis) were enrolled to group I (n=50), and group II (n=50) was composed of sepsis patients with a need for inotropes (septic shock). Diagnosis of sepsis and septic shock were made according to classical criteria (3).

Demographic data of the patients (including age, gender, BMI), baseline white blood cell count (WBC), hematocrit (hct), serum urea, creatinine, albumin levels, APACHE II and SOFA scores were recorded.

Heart rate, mean arterial pressure (MAP), central venous pressure (CVP), oxygen saturation (SaO_2), respiratory rate, peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2) values were also simultaneously recorded.

Body temperature was continuously monitored and recorded.

Radial artery was cannulated for blood gas analysis and procedure lasted for approximately 5 minutes. Blood samples for blood gas analysis were collected at the 1st, 2nd, 3rd, and 4th hours and pH, $PaCO_2$, PaO_2, SaO_2 were analysed with Cobas b 121™ (Mennheim, Germany).

$PtcO_2$ and $PtcCO_2$ were measured with Transcutaneous Combi M4 (TCM4)™ (Radiometer®, Copenhagen, Denmark) and were recorded simultaneously with the arterial blood sampling. Device was calibrated before inserting the transcutaneous blood gas probe in every patient. If unexpected alterations of recorded values were noticed, bio calibration was repeated. Conventionally, temperature of the electrode of TCM4™ was set to 43°C. The electrode of the TCM4™ was put on a hairless area of the forearm using a sticky fixation ring (E 5260/ E 5280: Fixation ring 904-891; 30 mm; Radiometer Medical ApS, Denmark) at the opposite side of the arm that arterial blood samples were obtained. A few beads of electrolyte solution (Electrolyte solution, Radiometer Medical ApS, Denmark) were dropped to establish a contact between the electrode and the skin. The localization of the electrodes remained constant during the study.

Inotropic indices of the patients in Group II were calculated according to the following formula depending on the vasoactive drug(s) used: Inotropic index = Dopamine* + Dobutamine* + (100 x Epinephrine*) + (100 x Norepinephrine*) + (15 x Milrinone*) (4).

(*µg/kg/min infusion rate)

Statistical Analysis

The normality of distribution of continuous variables was tested by Kolmogorov-Smirnov test. Student's t test was used for comparison of two independent groups of variables with a normal distribution and Mann-Whitney U test was used when the distribution was not normal. Paired-t test was utilized for comparison of two dependent groups of variables with normal distribution and Wilcoxon test was preferred when the distribution was not normal. The Chi-square test was used to assess relation between categorical variables and Pearson correlation coefficient was utilized for assessing relation between continuous variables. Descriptive statistic parameters were presented as frequency, percentage (%)

and mean ± standard derivation (mean ± SD). Statistical analysis was performed with SPSS for Windows version 11.5 ® and a p value < 0.05 was accepted as statistically significant.

Results

A hundred patients were enrolled to the study. Female to male ratios of group I and II were 24/26 and 25/25, respectively (p=0.841). Mean age of the patients in group I and II were 53.72±20.39 and 54.18±20.26, respectively (p=0.911). Also, BMI values of the patients in group I and II were 25.55±3.15 kg/m^2 and 25.05±3.10 kg/m^2, respectively (p=0.423).

There was no significant difference between groups in terms of baseline WBC (19062±13913/mm3 vs 19492±9573/mm3; p=0.857) and hct (30.94±5.77 % vs 31.66±6.40 %; p=0.556). Serum urea (80.16±49.75 mg/dL vs 122.54±71.89 mg/dL; p=0.003) and creatinine (1.42±1.32 mg/dL vs 2.38±1.70 mg/dL; p=0.001) levels were significantly higher, whereas albumin levels (2.94±0.47 g/dL vs 2.68±0.49 g/dL; p=0.008) were lower in Group II. APACHE II (28.26±4.84 vs 33.94±5.20; p=0.001) and SOFA (8.02±2.13 vs 10.64±2.53; p=0.001) scores were significantly lower in Group I.

Baseline heart rate (114.78±29.84 bpm vs 120.90±24.47 bpm; p=0.265) and CVP (3.96±2.81 cmH_2O vs 3.32±2.97 cmH_2O; p=0.272) values were not significantly different between the groups. Baseline MAP was significantly decreased in Group II compared with Group I (96.94±22.18 mmHg vs 76.36±17.49 mmHg; p=0.001).

There was no significant difference between groups in terms of body temperature (37.12 ± 1.03 0C vs 37.09 ± 1.42 0C; p=0.806).

Comparison of baseline respiratory rate (20.98±6.98/min vs 21.24±5.79/min; p=0.840) and PEEP (6.30±1.79 cmH_2O vs 6.76±2.03 cmH_2O; p=0.231) values was not statistically different between two groups. However, baseline PIP (15.34±5.03 cmH_2O vs 18.64±5.73 cmH_2O; p=0.003) and FiO_2 (0.502±0.19 vs 0.625±0.21; p=0.003) values were significantly decreased in Group I.

The pH values of patients in Group I were significantly higher than Group II at the baseline (7.41±0.08 vs 7.34±0.15, p=0.005), 1st hour (7.41±0.07 vs 7.34±0.15, p=0.004), 2nd hour (7.41±0.07 vs 7.34±0.14, p=0.004), 3rd hour (7.41±0.07 vs 7.34±0.14, p=0.004) and 4th hour (7.40±0.07 vs 7.34±0.14, p=0.003).

There was no significant difference between $PtcCO_2$ and $PaCO_2$ values analyzed simultaneously at baseline, 1st, 2nd, 3rd and 4th hours in Group I (Table 1).

$PtcCO_2$ values of group II were significantly lower when compared with $PaCO_2$ at baseline, 1st, 2nd, 3rd and 4th hours (Table 2).

$PtcO_2$ versus PaO_2 values were significantly lower in Group I at baseline, 1st, 2nd, 3rd and 4th hours (Table 3).

$PtcO_2$ vs PaO_2 values were significantly lower in Group II at baseline, 1st, 2nd, 3rd and 4th hours (Table 4).

There was a statistically strong positive correlation between arterial and transcutaneous CO_2 values in Group I at the baseline (r=0,972, p=0.001), 1st (r=0,971, p=0.001), 2nd (r=0,982, p=0.001), 3rd (r=0,986, p=0.001) and 4th (r=0,988, p=0.001) hours. There was a statistically similar strong positive correlation between arterial and transcutaneous CO_2 values in Group II at the baseline (r=0,983, p=0.001), 1st (r=0,976, p=0.001), 2nd (r=0,981, p=0.001), 3rd (r=0,981, p=0.001) and 4th (r=0,982, p=0.001) hours. Correlation between $PtcCO_2$ ve $PaCO_2$ alterations in Group I and Group II are shown on Figure 1.

Correlation analysis of arterial and transcutaneous O_2 values in Group I was performed and a statistically strong positive correlation was revealed at the baseline (r=0,815, p=0.001), 1st (r=0,881, p=0.001), 2nd (r=0,890, p=0.001), 3rd (r=0,863, p=0.001) and 4th (r=0,882, p=0.001) hours. A similar statistically strong positive correlation between

Table 1. $PtcCO_2$ and $PaCO_2$ values of patients in Group I.

Time	$PtcCO_2$ (Mean± SD)	$PaCO_2$ (Mean± SD)	p
Baseline	37.26±6.55	37.66±6.72	0.072
1st hour	37.10±6.11	37.60±6.24	0.231
2nd hour	36.86±6.11	37.03±6.42	0.332
3rd hour	37.12±5.96	37.12±6.07	0.967
4th hour	37.12±5.94	37.10±5.99	0.881

Table 2. $PtcCO_2$ and $PaCO_2$ values analyzed in group II

Time	$PtcCO_2$ (Mean± SD)	$PaCO_2$ (Mean± SD)	P
Baseline	34.64 ± 7.19*	39.00 ± 7.12	0.001
1st hour	34.76 ± 7.01*	39.04 ± 7.00	0.001
2nd hour	34.66 ± 6.89*	38.89 ± 6.79	0.001
3rd hour	34.58 ± 7.16*	38.96 ± 7.22	0.001
4th hour	34.44 ± 7.08*	38.92 ± 6.91	0.001

* Significant difference between $PtcCO_2$ and $PaCO_2$ values p<0.05

arterial and transcutaneous O_2 values in Group II was observed at the baseline (r=0,826, p=0.001), 1st (r=0,827, p=0.001), 2nd (r=0,659, p=0.001), 3rd (r=0,838, p=0.001) and 4th (r=0,834, p=0.001) hours. Correlation between $PtcCO_2$ ve $PaCO_2$ alterations in Group I and Group II are shown on Figure 2.

Inotropic index was 25.54±13.92 in Group II.

Table 3. $PtcO_2$ and PaO_2 values in group I

Time	$PtcO_2$ (Mean± SD)	PaO_2 (Mean± SD)	p
Baseline	66.16 ± 14.68*	82.87 ± 18.26	0.001
1st hour	70.20 ± 16.58*	86.65 ± 19.60	0.001
2nd hour	7158 ± 14.59*	88.13 ± 20.63	0.001
3rd hour	72.04 ± 13.05*	87.96 ± 18.19	0.001
4th hour	71.46 ± 12.90*	87.01 ± 17.06	0.001

*Significant difference between $PtcO_2$ and PaO_2 values p<0.05

Table 4. $PtcO_2$ and PaO_2 values in Group II

Time	PtcO2 (Mean± SD)	PaO_2 (Mean± SD)	p
Baseline	64,53 ± 17,12*	81,91 ± 21,53	0.001
1st hour	65,69 ± 17,21*	81,77 ± 20,35	0.001
2nd hour	66,66 ± 17,64*	80,64 ± 22,67	0.001
3rd hour	66,77 ± 17,64*	81,56 ± 19,76	0.001
4th hour	66,47 ± 17,65*	80,47 ± 18,05	0.001

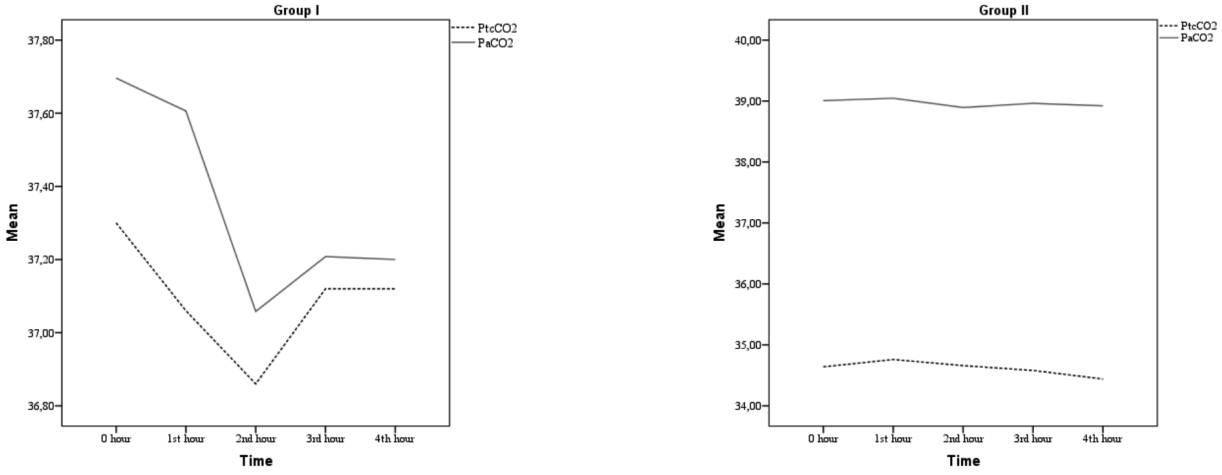
*Significant difference between $PtcO_2$ and PaO_2 values p<0.05

Discussion

Septic patients have compromised tissue perfusion due to microcirculatory disturbances. Impaired tissue microperfusion of patients with septic shock had been clearly shown in previous studies. In general, macro circulatory parameters are the main targets in order to optimize treatment of septic shock in early phase (5). However, persistent compromisation of tissue perfusion may occur in some patients due to microcirculatory disturbances. Although conventional blood gas sampling methods are considered as "gold standard", there is always place for a less invasive, painless, and timesaving "patient-friendly" alternatives. There are many papers implicating the cons of unnecessary blood draws with respect to not only anemia but also infection control and healthcare costs (6,7). Therefore the need for less invasive monitoring methods is evident.

In the English literature there are recent papers regarding comparison between non-invasive $PtcO_2$ / $PtcCO_2$ monitoring and conventional blood gas sampling methods such as in neonatal and adult intensive care units (8-10), but to the best of our knowledge this is the first prospective study comparing the transcutaneous O_2 and CO_2 analysis versus arterial blood gas analysis in a homogenous specific subgroup such as septic patients in ICU and also one of the largest sample size.

There are three major results arising from this study. First, there was no significant difference between the values of $PtcCO_2$ and $PaCO_2$ in patients with sepsis. There was



*p values for baseline, 1st, 2nd, 3rd and 4th hours are 0.072, 0.231, 0.332, 0.967 and 0.881

*p values for baseline, 1st, 2nd, 3rd and 4th hours are all 0.001.

Figure 1. Correlation between $PtcCO_2$ and $PaCO_2$ alterations in Group I and Group II

a strong positive correlation between $PtcCO_2$ and $PaCO_2$ values (Figure 1). These findings may support to use $PtcCO_2$ monitoring as an acceptable alternative method.

Second, $PtcCO_2$ values of Group II were significantly lower than $PaCO_2$ values ($p<0.05$) and there was a strong positive correlation between the values indeed. This finding is not surprising because abolished peripheral microcirculation is a part of the septic shock pathophysiology itself. Hypo perfusion states like shock and/or acidosis may present decreased values of $PtcO_2$ and $PtcCO_2$ and vasoactive drug administration may also result in decreased $PtcO_2$ and $PtcCO_2$ (11-14).

Recent TCM™ devices with the help of selection of a sensor place near the carotid artery have led to improved correlation between PaO_2 and $PtcO_2$ measurements (15-18). Studies regarding placement of the sensor site on the distal part of an extremity have reported lower readings, due to vasoconstriction limiting blood flow (19-21). Other studies have shown that choosing a sensor area in chest, infraclavicular area or ear is accompanied with more reliable results (22,23). In this present study, the sensor was placed in the forearm, which can be accepted relatively a distal part of the extremity, and therefore might have contributed to the lower reading of $PtcCO_2$ values in patients with septic shock. Although we demonstrated strong positive correlation between simultaneously obtained $PtcCO_2$ and $PaCO_2$ values, this may be accepted as a limitation of the study. This unexpected finding of our study also emphasizes the importance of correct selection of sensor electrode placement, especially when the pathophysiology of septic shock is considered.

Third, simultaneously measured values of $PtcO_2$ were significantly lower than PaO_2 and there were strong positive correlations in both study groups. This finding is consistent with the literature. The more the skin is warmed to highest tolerable temperature, the more increase takes place in the capillary blood flow. In order to reach the greatest increased blood flow, the highest tolerable temperature is reported as 45 °C, when the surface blood $PtcO_2$ rises to approximately PaO_2 (24). There is a generally accepted rule for safety as limiting the electrode temperature at 43°C up to four hours, although suggested monitoring method for detection of $PtcCO_2$ and $PtcO_2$ is to increase the skin temperature up to 45 °C to arterialize capillary blood flow (25, 26). However, higher electrode temperatures may generate the risk of skin burning. In our study, we limited the electrode temperature at 43°C for safety, which is appropriate for detecting $PtcCO_2$, but not for $PtcO_2$. Our concerns regarding safety instead of increasing the temperature of the electrodes for more accurate measurements seems to be another dilemma when interpreting our results.

Another explanation for the lower detected values of $PtcO_2$ in both groups may be impaired macro and microcirculation, which is similar to $PtcCO_2$.

Conclusions

In summary, transcutaneous monitoring of CO_2 may be a charming, less-invasive, time-consuming and reliable alternative method in patients with sepsis. The effectiveness and safety of this method in patients with septic shock is

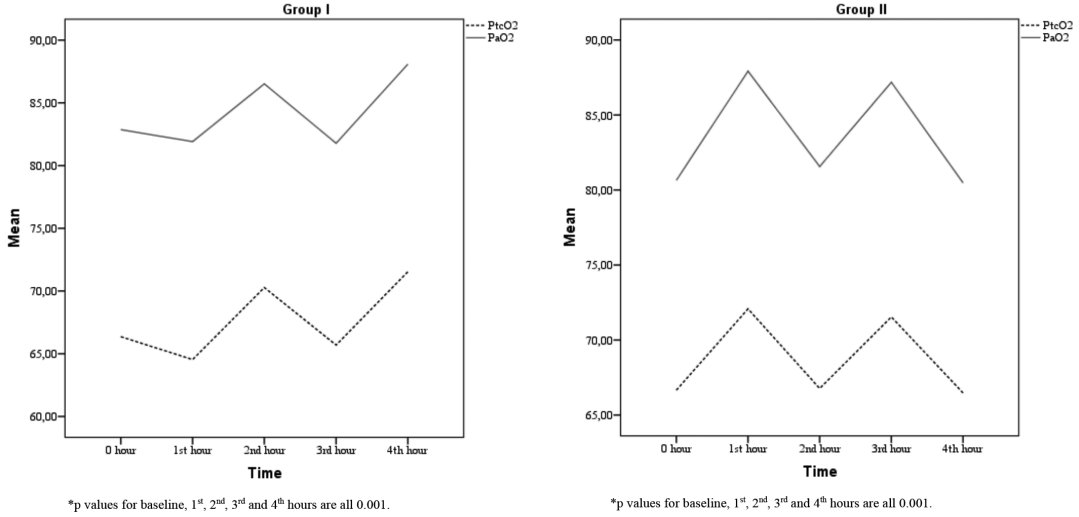


Figure 2. Correlation between $PtcO_2$ and PaO_2 alterations in Group I and Group II

questionable. Transcutaneous monitoring of O_2 may not be a reliable and feasible method for patients with sepsis and septic shock. The need for further large scaled studies is evident to confirm the safety, effectiveness and optimization of these recent techniques of transcutaneous CO_2 and O_2 monitoring.

Ethics

Ethics Committee Approval: Approval of the study has been obtained from the ethical committee of the faculty (Approval no: 249).

Informed Consent: All the patients and/or their relatives were informed verbally and also written consent were obtained.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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