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What is the Diagnostic Value of Plasma Antioxidative/Oxidative Status in Parapneumonic Effusions in Children?

Parapnömonik Efüzyonlu Çocuklarda Plazma Antioksidatif/Oksidatif Seviyelerinin Tanı Değeri Nedir?

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ABSTRACT Objecive: Pleural effusions are associated with high morbidity in children. Oxidative stress, which refers to an imbalance between oxidants and antioxidants, is associated with various diseases including lung diseases. The aim of this study was to investigate to the total oxidative status (TOS) and total antioxidative status (TAS) in differentiating exudates from transudates in children. **Material and Methods:** In this cross-sectional study, data from patients who were hospitalized for parapneumonic effusions and underwent thoracentesis from October 2012 to December 2013 in the pediatric surgery department. The patiens were divided into two groups (the exuda and transude groups) according to Light's criteria. Blood plasma and parapneumonic effusions were analyzed and compared with respect to the total antioxidative and oxidative status. **Results:** The study consisted of blood plasma and pleural effusion from 40 children with parapneumonic effusions (PPEs) (transude group [n=20]; exuda group [n=20]) and just blood plasma from 30 healthy children (control group). There were no significant difference between the groups in terms of gender and age. The blood plasma TAS level of the control group was significantly higher than the level of blood plasma TAS level of the exuda and transude groups with statistically significant ($p<0.001$). The value of plasma oxidative stress index (OSI) and TOS of exuda group were significantly higher than those of the control and transude groups with statistically significant ($p<0.05$). **Conclusion:** This study suggests that inflammation is associated with PPE in children that increased OSI in blood plasma from PPE patients is related to tissue damage and turnover.

Keywords: Child; exudates and transudates

ÖZET Amaç: Plevral efüzyonlar çocuklarda yüksek morbidite ile ilişkilidir. Oksidatif stres, oksidanlar ile antioksidanlar arasındaki dengesizliği ifade eder ve akciğer hastalıkları dahil biçok hastalıkla ilişkilidir. Bu çalışmanın amacı, çocuklarda transüda ve eksüdaların ayırıcı tanısında toplam oksidatif durumun (TOS) ve total antioksidatif durumun (TAS) yararlılığını araştırmaktır. **Gereç ve Yöntemler:** Bu çalışmada kesitsel olarak Ekim 2012'den Aralık 2013'e kadar parapnömonik efüzyon nedeniyle çocuk cerrahisi bölümüne başvuran ve torasentez yapılan hastalardan elde edilen veriler sunulmuştur. Light kriterlerine göre hastalar iki gruba ayrıldı (eksudatif ve transudatif). Kan plazması ve parapnömonik efüzyonlar analiz edilip ve toplam antioksidatif ve oksidatif duruma göre karşılaştırıldı. **Bulgular:** Bu çalışma, 30 sağlıklı çocuğun (kontrol grubu) kan plazmasını, 40 parapnömonik efüzyonlu (PPE) hastanın; (transüda grubu [n=20], eksüda grubu [n=20]) kan plazmasını ve pleural efüzyonu içermektedir. Cinsiyet ve yaş açısından gruplar arasında anlamlı fark yoktu. Kontrol grubunun kan plazma TAS seviyesi eksüda ve transüda grupların kan plazma TAS düzeyinden anlamlı derecede yüksekti ($p <0.001$). Eksüda grubun plazma oksidatif stres indeksi (OSİ) ve TOS değerleri, kontrollere ve transüda efüzyonlu hastalardan anlamlı derecede yüksekti ($p <0.05$). **Sonuç:** Bu çalışmada PPE hastaların kan plazmasındaki artan OSI değeri doku inflamasyonu ve doku hasarı ile ilişkili olduğunu göstermektedir.

Anahtar Kelimeler: Çocuk; eksüda ve transüda

Pleural effusions accumulate when the rate of pleural fluid formation exceeds the ability of the parietal pleural lymphatics system to remove fluid from the pleural space between the lung and chest wall.[1,2] This space normally contains just a small amount of fluid (0.26±0.1 ml/kg).[3-5] Although there are many causes of pleural effusions, including heart failure, trauma, liver disease, and malignancy, in the pediatric population, they are most commonly caused by infection.[1,5-7] Parapneumonic effusions (PPEs) or empyema affect 2–12% of children with pneumonia.[1,4] PPEs should always be suspected in patients with pneumonia who fail to respond to antibiotics, and 13% of PPEs eventually require surgery.[3] Patients who present with a pleural effusion for the first time should undergo diagnostic thoracentesis to determine whether it is exudative or transudative.[8,9] Light's criteria are generally used for this purpose.[9] These criteria are based on the concomitant measurement of protein and lactate dehydrogenase (LDH) in both pleural fluid and serum. Since they were developed in 1972, they have been routinely adopted in clinical practice for distinguishing transudates from exudates.[1,2,5,6] In the last decade, many alternatives to Light's criteria have been proposed for differentiating transudates and exudates.[3] These include complement, neutrophil-derived enzyme, proinflammatory and anti-inflammatory cytokine, acute-phase reactant, and other miscellaneous tests.[3]

The lung represents a unique tissue in both its exposure to higher oxygen tension and high concentration of antioxidants.[8] Normal physiological functions depend on a balance between oxidants and antioxidants in the lung, and both excess production of oxidants or depletion of antioxidants can disrupt this balance.[10,11] Such an imbalance results in oxidative stress, which is implicated in the etiopathogenesis of several inflammatory lung diseases.[10] The exact mechanism of the imbalance between oxidants and antioxidants in pleural effusions is unclear. In some cases of pleural effusions, oxidants increase and antioxidants decrease. In such cases, antioxidative mechanisms may be insufficient to prevent oxidative damage.[10]

The aim of the present study was to evaluate the levels of total oxidative status (TOS), total antioxidative status (TAS) and oxidative stress index (OSI) in blood plasma of pediatric patients with pleural effusions after pneumonia and compare the usefulness of these parameters in distinguishing transudates and exudates.

MATERIAL AND METHODS

This cross-sectional study involved patients were undergoing thoracentesis for the definitive diagnosis of PPE admitted to our pediatric surgery department between October 2012 and December 2013. Although patients in the control group had also presented to the hospital, they had no health problems, and they or their parents consented to their participation as controls.

The inclusion criteria were a history of pneumonia and with PPE (presence of pleural fluid upon ultrasonography examination). Age between 0 and 16 years, and permission from the patient's parent to participate in the study.

The exclusion criteria were no signed informed consent from the patient's parent prior to entry into the study. The causes of pleural effusion except pneumonia such as heart failure, malinancy and other cases.

The parents of each participating child gave informed written consent for participation, and each child gave oral consent to participation prior to the intervention. The study was carried out in accordance with the Helsinki Declaration as revised in 1989 and approved by the local human institutional review committee. The study protocol is approved by the our University Ethics Committee with no:B.30.2.HRÜ.0.20.05.00.050.01.04-74.

All the patients underwent the same procedure; thoracentesis procedure was done under local anesthesia and guided by ultrasonography, with sedation provided by ketamine. The same surgeons performed all the procedures. Pleural fluids samples were classified as exudates or transudates according to Light's criteria. *Exuda group*; when the fluid properties met at least one of Light's criteria (ratio of pleural fluid to serum protein greater than

0.5, ratio pleural fluid to serum LDH greater than 0.6, or a pleural LDH level over 2/3 of the serum LDH *Transude group;* characterized by ratio of pleural fluid to serum protein less than 0.5, ratio pleural fluid to serum LDH less than 0.6. or a pleural LDH level less 2/3 of the serum LDH. The exuda group of patients are treated at the pediatric surgery department with tube thoracostomy at the initial treatment. The transude group of patients were referee to the pediatric clinic.

SAMPLE COLLECTION

Pleural fluid (10 cc) was obtained by thoracentesis following a clinical and radiological examination of the patient. A hemogram was obtained for each patient, and LDH, total protein, and albumin levels were determined in pleural effusions and blood samples. Cell counts were obtained, and gram staining, nonspecific aerobic culture, and Ziehl–Neelsen staining were performed.

At the same time, 4 cc of blood and pleural fluid were collected from the patients, placed in empty tubes, and stored on ice at 4° C. The samples were collected for measurement of TOS, TAS, and OSI levels. The plasma and pleural effusions were then separated from the cells by centrifugation at 3000-5000 rpm for 5 min. The serum and pleural fluid samples that were obtained were stored at -80° C for combined measurement of TOS, TAS, and OSI. An Abbott Aeroset auto-analyzer device was used for the measurements.

TAS, TOS, AND OSI MEASUREMENTS

TAS levels in the samples were measured using a Rel Assay commercial kit. The results were reported as mmol Trolox equivalents/L.[12] TOS levels in the samples were measured using a Rel Assay commercial kit (Mega Tip, Gaziantep, Turkey). The colorimetric method was used to evaluate the cumulative oxidation of ferrous ions to ferric ions by oxidant molecules. The results were expressed as μmol H_2O_2 equiv/L.[13] The OSI, which is an indicator of oxidative stress, was calculated as the TAS percentage of the TOS level. The results were expressed as arbitrary units.[14]

STATISTICAL ANALYSIS

The SPSS for Windows 11.0 (SPSS Inc., Chicago, IL) program was used for the statistical analysis. The Student's *t*-test and a one-way ANOVA were used for the comparison of descriptive statistical data (mean, standard deviation), as well as quantitative data for parameters with a normal distribution. Light's criteria were used to detect cut-off points of transudate and exudate values. Pearson's correlation analysis was used to determine the relationship between TAS, TOS, and OSI. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

In this study, effusion and blood samples were the exuda group (n=20), the transude group (n=20) and just blood sample was collected from the control (n=30) who presented to the hospital for other reasons and they don't have any health problem.

When the demographic data of the groups were evaluated, there were no significant differences in the average age and gender of the exuda, transude and control groups (Table 1).

Using 0.6 as a cut-off value of the pleural effusion/serum LDH ratio, all the transudate cases were below this value. When a PPE/serum total protein ratio cut-off value of 0.5 was applied, all the exudative cases were above this value, whereas all the transudative cases were below this value. In this study, mostly (80%) LDH ratio was used.

TABLE 1: Demographic data of the patients in the exuda, transude and control groups.

	Exudative (n=20)	Transudative (n=20)	Control (n=30)	P Value
Gender Male/ Femal	12/8	10/10	23/7	0,139
Age (years)	7,70 ± 4,60	5,60 ± 2,72	6,43 ± 1,97	0,109

The plasma TAS level of the control group was higher than the plasma TAS levels of the exuda and transude groups with statistical significance (p<0.001). When the TOS levels of the three groups were compared, the TOS levels of the exuda and transude groups were higher than those of the control group with statistical significance (p<0.01). The plasma TOS level of the exuda group was higher than that of the transude group however there were no statistical significant differences (p>0.5).

The plasma OSI level of the exuda and transude groups were higher than that of the control group with statistical significant differences. The plasma OSI level was significantly higher in the exuda group than in the transude group with statistical significance (p<0.001) (Figure 1). The results of the comparison of the plasma TAS, TOS, and OSI values are illustrated in (Table 2).

When the TAS levels of the exuda and transude in the PPE groups were compared, the levels were found to be higher in the transude pleural effusions however there were no statistical significant differences (p>0.05), as illustrated in (Figure 1). As regards the TOS levels of the PPE groups, these were higher in the exude group than however there were no statistical significant differences (p>0.05).

When the OSI levels of the exuda and transude were compared in the PPE groups, the OSI level of the exuda group was higher than that of the transude group however there were no statistical significant differences (p>0.05; (Figure 2).

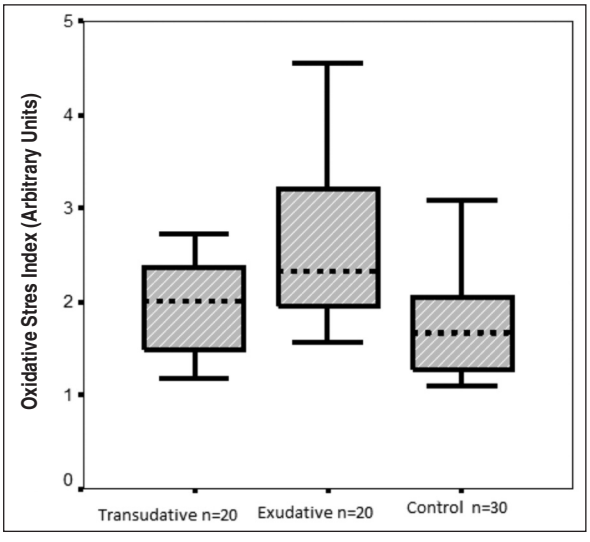

FIGURE 1: The oxidative stress index (OSI) of blood plasma used for differentiation between transudate and exudate and control groups.

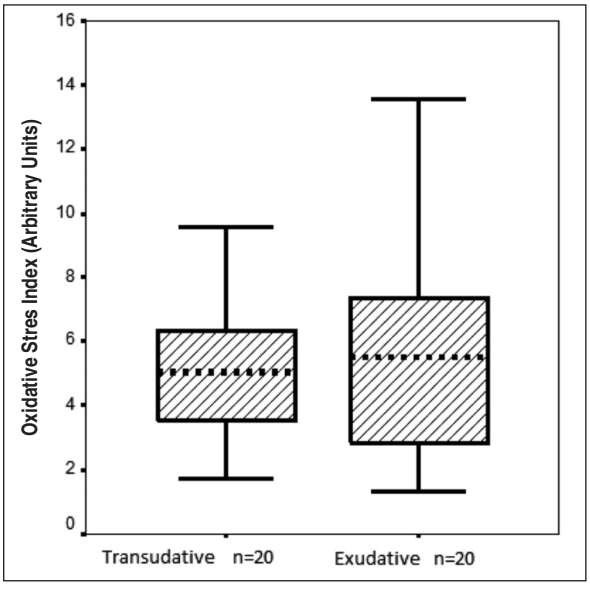

FIGURE 2: The differentiation of oxidative stress index (OSI) between exudate and transudate groups for pleural fluid.

TABLE 2: The comparison of oxidative and antioxidative parameters of plasma of exudate, trasudate and control group.

	Exudative (n=20)	Transudative (n=20)	Control (n=30)	P Value
TAS (mmol Trolox Eqv: /L)	0,58 ± 0,10^{a***,b***}	0,71 ± 0,15	0,78 ± 0,14	<0,000
TOS (µmol H_2O_2 Eqv./L)	14,88 ± 4,26^{b}	13,48 ± 2,36	12,38 ± 1,99	0,0,16
OSI (Arbitrary Unite)	2,62 ± 0,89^{a***b***}	1,96 ± 0,52	1,70 ± 0,47	<0,000

a: There were significant differences between Exudative and Transudative groups

b:There were significant differences between Exudative and Control groups.

***: p ≤ 0,001

**: p ≤ 0,01

*: p ≤ 0,05

TABLE 3: The comparison of oxidative and antioxidative parameters of pleural fluid of exudate group and transudate group.

	Exudative (n=20)	Transudative (n=20)	*P* Value
TAS (mmol Trolox	0,059 ± 0,18	0,073 ± 0,026	0,055
TOS (μmol H2O2	3,63 ± 1,70	2,82 ± 1,04	0,081
OSI (Arbitrary	5,58 ± 3,30	5,08 ± 2,12	0,576

The level of oxidative parameters were found to be higher in the transude pleural effusions (Table 3).

DISCUSSION

The present study investigated potential differences in the TOS, TAS, and OSI levels of transudates and exudates of PPEs in children as compared to findings obtained using Light's criteria. The plasma TOS and OSI levels of patients with exudative pleural effusions were significantly higher than those of patients with transudative pleural effusions and controls. The TAS was higher in transudative than exudative pleural effusions in children. This is the first report to compare the TAS, TOS, and OSI levels of children with PPEs.

PPEs are a common pediatric phenomen on worldwide. Therefore, many previous studies have focused on PPEs. The transudate/exudate distinction for planning thoracotomy/oscopy for the treatment of PPE .Transudates result from increased hydrostatic pressure and decreased oncotic pressure. In the case of transudates, the pleural surface is structurally intact and acts as a passive membrane, following Starling's law.[2,4,7] In contrast, with exudates, the pleural surface is inflamed, resulting in increased capillary permeability.[2,5] The first step in distinguishing transudates and exudates in a patient with pleural effusions is a differential diagnosis by an examination of pleural fluid, imaging, or even invasive procedures.[1,5,7] As reported earlier, the most commonly used approach for defining the presence of an exudative effusion is Light's criteria, with 99% sensitivity and 98% specificity for identifying exudates and 73% sensitivity and specificity for identifying transudates.[2,5-7] Validation studies confirmed the high sensitivity of Light's criteria but low specificity. The low specificity was reported to be particularly prevalent in heart failure patients receiving diuretics, which remove more water than proteins and LDH from the pleural space.[9] A high pleural fluid erythrocyte count, which can raise the pleural LDH level, in heart failure patients was reported to be another potential source of an incorrect exudate diagnosis, as well as the albumin gradient in patients with other conditions.[2,9]

A modified version of Light's criteria utilized pleural fluid cholesterol and albumin as markers to differentiate between transudative and exudative pleural effusions.[7] In addition, the amino terminal fragment of pro-brain natriuretic peptide and the leukocyte count have been employed to differentiate between pleural effusions in PPEs.[7,9] The aim of the present study was increase the specificity of Light's criteria. According to Light's criteria, in exudates, the ratio of pleural fluid to serum LDH is 0.6 higher than the upper limit.[2] The present study utilized mostly this value in classifying the pleural fluid.

Many tests are available to identify differences between exudates and transudates, some of which utilize serum procalcitonin and C-reactive protein in the differential diagnosis of pleural effusions. Previous research reported that the specificity and sensitivity C-reactive protein for pleural effusions were higher than the specificity and sensitivity of procalcitonin.[15] Calprotectin, tumor necrosis factor alpha, and C-reactive protein were also shown to be useful in the diagnosis of exudative pleural effusions.[15,16] High levels of serum amyloid alpha were observed in the exudate of patients with PPEs but subsequently disappeared following the development of pleural thickening.[17] The level of is-

chemia-modified albumin was reported to be a marker in pleural effusions, with higher levels in transudative than exudative effusions. However, blood levels of ischemia-modified albumin were not significant in transudates and exudates.[18] However, as compared with Light's criteria, most of the aforementioned parameters are not suitable because they are not supported in routine practice, the tests are not easy to perform, and the results are not rapid.

As the oxidative and antioxidative capacity is easy to measure and apply, we think that this measurement may be suitable for children with PPEs. Although many diseases cause changes in oxidative stress levels, the nature of the relationship between oxidative stress and PPEs is unknown. The lung is exposed to high level of oxygen, which together with its large surface area and blood supply, make it susceptible to injury, mediated by radical oxygen species.[10,19] Oxidative stress causes oxidation of proteins, cell membrane damage, direct DNA methylation, and lipid peroxidation. In addition, it plays a critical role in inflammatory responses in lung diseases through the upregulation of redox-sensitive transcription factors, resulting in enhanced expression of proinflammatory genes.[19-22] This results in extensive cellular and tissue damage and contributes significantly to worsening of lung infection responses by decreasing the antioxidant capacity.[19-22] In this way, oxidative stress can affect remodeling of the extracellular matrix, mitochondrial apoptosis, cell proliferation, alveolar repair, and immune modulation.[20-23] Therefore the test of TAS, TOS, and OSI level may useful for distinguishing exudates and transudates in PPEs.

The production of reactive oxygen species in the mitochondria occurs as a by product of oxidative phosphorylation by the mitochondrial electron transport chain. An increase in the oxidant capacity or decrease in the antioxidant capacity influences cellular processes and mitochondrial apoptosis, inducing inflammation and affecting the innate immune system.[23] An inadequate antioxidant capacity can indicate increased oxidant-induced tissue injury.[21] Accordingly, increased permeability of the lung in patients with PPEs allow the transport of inflammatory mediators, pleura fluid and proteins. As shown in a previous study of children with acute pneumonia, enzymatic and nonenzymatic antioxidant activity decreased and oxidative stress increased.[24] Serum TAS was also reported to be decreased in pneumonia patients, with the decline associated with increased severity of the disease.[25] Antioxidant molecules can prevent or inhibit the aforementioned harmful reactions. Although serum concentrations of different antioxidants can be measured separately, the measurement of TAS is more practical .[14] A previous study showed that pneumonia increased the oxidant burden through the release of bacterial components to the epithelial surface of the lung.[22] The airway epithelium serves as an effective antioxidant defense system. However, oxidative stress-induced cell membrane damage, lipid peroxidation, and DNA methylation, which result in extensive cellular and tissue damage and significant worsening of lung infections, adversely affect this protective barrier.

In the present study, when the plasma TAS values of the three groups were compared, they were highest in the transudate effusions and lowest in the exudate effusions. The TOS and OSI values of plasma of exudates were higher than plasma of transudates and plasma of controls, with the lowest values in the control group. In the PPE groups, the OSI value of exudates was higher than the OSI value of transudates.

OSI may be directly or indirectly regulate histone modifications, such as acetylation, methylation, and phosphorylation, causing of increased expression of inflammatory mediators.[24] Therefore the level of OSI more sensitive than level of TAS and TOS The level of antioxidant/oxidant differences in pleural fluid is correlate with plasma level however more sensitif because of the differences of antioxidant and oxidant capacity maybe related more systemic respond than lokal respond.

The present study has some limitations. First, the data on TAS, TOS, and OSI levels may be limited only to children with PPEs and not be rep-

resentative of those seen in other conditions. Second, the sample sizes in each group were small and may not be large enough for the results to have had sufficient statistical power to detect differences. Thus, it cannot be concluded that OSI, TAS, and TOS levels should be the first line of investigation in studies aimed at distinguishing pleural effusions or that they are better than Light's criteria for PPEs. Future controlled clinical trials are needed to support and extend the data.

CONCLUSION

TOS and OSI levels were indicative of oxidative stress in PPEs, and they were higher in exudates of PPEs and correlated with blood levels. The level of plasma OSI in PPEs may be a diagnostic parameter in distinguishing transudate and exudates, in addition to Light's criteria. The level of differences antioxidant and oxidant capacity maybe helpful for diagnosis and fellow up pneumonic patients. Further studies with a larger sample size are needed to define the role played by antioxidants in the in the progression of parapneumonic patients.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

All authors contributed equally to this study.

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