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The Value of Serum Ischemia Modified Albumin Levels on Diagnosing Pediatric Testicular Torsion and Predicting Testicular Atrophy After Operation

Pediatrik Testis Torsiyonunun Tanısında ve Ameliyat Sonrası Testis Atrofisinin Öngörülmesinde Serum İskemi Modifiye Albümin Düzeylerinin Değeri

Oktay Ulusoy[1], Müge Şencan[1], Ayten Bilen[1], Emel Ulusoy[2], Tuncay Küme[3], Oğuz Ateş[1], Gülce Hakgüder[1], Mustafa Olguner[1], Miraç Feza Akgür[1]

[1]Dokuz Eylül University Faculty of Medicine, Department of Pediatric Surgery, İzmir, Türkiye
[2]Dokuz Eylül University Faculty of Medicine Department of Pediatrics, Division of Pediatric Emergency Care, İzmir, Türkiye
[3]Dokuz Eylül University Faculty of Medicine, Department of Biochemistry, İzmir, Türkiye

Abstract

Introduction: To clinically investigate the value of serum ischemia modified albumin (IMA) levels on diagnosing pediatric testicular torsion (TT) and predicting testicular atrophy after operation.

Methods: This prospective case control study was conducted between June 2021 and January 2023. Patients aged 1-18 years who were evaluated for acute scrotum and diagnosed as TT based on clinical and radiological evaluations were included in the study. Demographic data, clinical features, radiological findings, serum IMA levels, operative findings, short and long-term complications, follow-up were recorded.

Results: The serum IMA levels of patients who underwent operation due to TT were statistically significantly higher compared with the control group (p<0.001). Receiver operating characteristic analysis revealed an optimal cut-off point at 18.90 ng/mL for separating the TT group from the control group. When patients who underwent orchiectomy during surgery were compared with those who developed testicular atrophy after detorsion, no statistically significant difference was found in terms of serum IMA levels (p=0.857). Serum IMA levels in patients who underwent orchiectomy during surgery and in patients who developed testicular atrophy after detorsion were significantly higher than in patients without complications (p=0.013 and p=0.012, respectively).

Öz

Giriş: Pediatrik testis torsiyonu (TT) tanısında ve operasyondan sonra testis atrofisini tahmin etmede serum iskemi modifiye albümin (IMA) düzeylerinin değerini klinik olarak araştırmak.

Yöntemler: Bu prospektif olgu kontrol çalışması Haziran 2021 ile Ocak 2023 arasında yürütülmüştür. Akut skrotum açısından değerlendirilen, klinik ve radyolojik değerlendirmelere dayanarak TT tanısı konulan 1-18 yaş arası hastalar çalışmaya dahil edilmiştir. Demografik veriler, klinik özellikler, radyolojik bulgular, serum IMA düzeyleri, operasyon bulguları, kısa ve uzun dönem komplikasyonlar, takip kaydedildi.

Bulgular: TT nedeniyle operasyon geçiren hastaların serum IMA düzeyleri kontrol grubuna kıyasla istatistiksel olarak anlamlı derecede yüksekti (p<0,001). İşaret karakteristiği eğrisi analizi, TT grubunu kontrol grubundan ayırmak için optimum cut-off noktasının 18,90 ng/mL olduğunu ortaya koymuştur. Ameliyat sırasında orşiektomi uygulanan hastalar detorsiyondan sonra testis atrofisi gelişen hastalarla karşılaştırıldığında serum IMA düzeyleri açısından istatistiksel olarak anlamlı bir fark bulunmamıştır (p=0,857). Ameliyat sırasında orşiektomi uygulanan hastalarda ve detorsiyondan sonra testis atrofisi gelişen hastalarda serum IMA düzeyleri komplikasyonsuz hastalara göre anlamlı derecede yüksek bulunmuştur (sırasıyla p=0,013 ve p=0,012).

Address for Correspondence/Yazışma Adresi: Oktay Ulusoy M.D., Dokuz Eylül University Faculty of Medicine, Department of Pediatric Surgery, İzmir, Türkiye
E-mail: oktay.ulusoy@deu.edu.tr **ORCID ID:** orcid.org/0000-0002-0992-8724
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Abstract

Conclusion: In the present clinical study, we found that serum IMA levels are a valuable molecule in the diagnosis of childhood TT, in predicting testicular atrophy, and therefore in the decision for intraoperative orchiectomy.

Keywords: Pediatric, testicular torsion, ischemia modified albumin

Öz

Sonuç: Mevcut klinik çalışma sonucunda serum IMA düzeylerinin çocukluk çağı testis torsiyonunun tanısında, testis atrofisini tahmin etmede ve dolayısıyla intraoperatif orşiektomi kararında değerli bir molekül olduğu sonucuna vardık.

Anahtar Kelimeler: Pediatrik, testis torsiyonu, iskemi modifiye albümin

Introduction

The most common cause of acute scrotum requiring operative treatment is testicular torsion (TT). TT results from twisting of the spermatic cord around its longitudinal axis, causing impairment of blood flow to the testis that may cause testicular necrosis.[1] If detorsion is performed within the first 6 hours after onset of pain, 90-100% testes may be saved. However, if detorsion is performed within 12-24 hours after onset of the pain, the chance of saving the testis has been shown to decrease below 10%.[2] Operative intervention must be performed promptly to avoid loss of function of the ipsilateral testis.[3]

Several biomarkers to determine the permanent testicular ischemic damage after TT have been studied.[4-6] Ischemia modified albumin (IMA) has become a prominent biomarker in recent years regarding the role of ischemia especially for pediatric appendicitis.[7,8] IMA is a useful and well-known biomarker for ischemia. The last amino-terminal end of albumin is the region where the transitional metals such as cobalt, copper, and nickel are bound. Hypoxia, acidosis, free radical damage, and membrane deterioration reduce the binding capacity of the transitional metals and result in a change in the structure of albumin.[9] Experimental studies have shown that serum IMA levels increase after TT.[10-12] To the best of our knowledge serum IMA levels after TT has not been studied clinically. We hypothesized that IMA may be useful during diagnosing pediatric TT, decision making for intraoperative orchiectomy and for predicting postoperative testicular atrophy in pediatric TT.

In current study, we aimed to clinically investigate the value of serum IMA levels on diagnosing pediatric TT and predicting testicular atrophy after operation.

Materials and Methods

This prospective case control study was conducted between June 2021 and January 2023. The study protocol was designed in compliance with the Declaration of Helsinki. Informed consent was obtained from parents or legal guardians before enrollment in the study. The study was approved by the Dokuz Eylül University Non-Interventional Research Ethical Committee (decision no: 2022/03-11, date: 19.01.2022). Patients aged 1-18 years who were evaluated for acute scrotum with diagnosed as TT based on clinical and radiological evaluations were included in the study. Patients with an acute scrotum and presence of decreased and/or absent blood flow on Doppler ultrasonography (US) but no torsion detected during surgery were excluded from the study as this exclusion may change the IMA results. Demographic data, clinical features, radiological findings, serum IMA levels, operative findings, short and long-term complications, and follow-up were recorded.

TT was diagnosed based on medical history, physical examination, gray scale and Doppler US findings. General electric (GE) Logiq S7 (GE Healthcare, Milwaukee, WI) US equipment were used in present study. All gray scale and Doppler US examinations were performed by radiologists with pediatric radiology experience. Redundant spermatic cord, testicular swelling, testicular parenchymal anatomy and hydrocele were evaluated with gray scale US. The Doppler signal (decrease or absence) of the testis and rotation of the spermatic cord were evaluated. In presence of decreased and/or absent blood flow on Doppler US i.e., consistent with TT, an immediate operative intervention was performed.

The patients were divided into 2 groups.

Control group (n=31): Comprised of healthy patients undergoing circumcision under general anesthesia.

TT group (n=21): Patients who underwent operation due to TT.

The TT group was divided into three subgroups based on the surgical outcomes and follow-up results;

TT requiring orchiectomy (n=4): Refers to patients who underwent intraoperative orchiectomy.

No testicular atrophy after operative detorsion (n=14): Patients who underwent operative detorsion and had no testicular atrophy during follow-up.

Testicular atrophy after operative detorsion (n=3): Patients who developed testicular atrophy during follow-up after operative detorsion.

Operative Technique

The inguinal approach was preferred as standard in all patients. Testicular detorsion and testicular fixation were performed in patients in whom testicular blood flow improved after wrapping the testes with warm moist swabs. Orchiectomy was performed in patients in whom no testicular blood flow improvement was observed after wrapping testes with warm moist swabs.

Biochemical Analysis

Blood samples and IMA were collected on admission to pediatric emergency department. Serum IMA levels were measured before surgery. Serum samples for IMA analysis were stored at -80 °C until analysis. Serum IMA levels (cat no: CSB E09594h, Elabscience Biotechnology Co, Wuhan, China) were measured using an enzyme-linked immunosorbent assay (ELISA) kit based on the principle of sandwich enzyme immunoassay. Since the ELISA test gives results in a minimum of two days, IMA values were not used for surgical indication in any patient. Informed consent was obtained from all patients before blood samples were taken.

Statistical Analysis

Statistical analysis was performed using SPSS 24.0 (IBM Corp. Armonk NY, USA). Data are presented as median with interquartile range and 25^{th}-75^{th} percentiles. Histograms were used to assess the normality of sample distributions. The Kruskal-Wallis test was used for analyzing plasma IMA levels among different groups. The Mann-Whitney U test was used for post-hoc comparisons. All t-tests were two-tailed, and group differences or correlations with $p<0.05$ were considered to be statistically significant. Receiver operating characteristic (ROC) analysis was used to detect the optimal cut-off points for separating the TT group from the control group and TT with orchiectomy from TT without orchiectomy. Spearman's ρ test was used to assess the correlation between IMA and the duration of symptoms.

Results

Twenty-one patients with TT and 31 control patients were enrolled. For of TT patients at the time of operation was 13 years (13.10-14.75 years), the median age of the control group was 11 years (9-15 years). There is no statistically significant difference regarding age between the groups (p=0.482).

Left TT was present in 12 (57.1%) patients. The median duration of symptoms was 14 hours (6-42 hours). The most common clinical features were scrotal pain, followed by scrotal swelling, with edema and absence of cremasteric reflex, which were equally common. The clinical features are summarized in Table 1. Gray scale and Doppler US were performed in all cases. With US; increased ipsilateral testis size was detected in 18 patients (85.7%), and ipsilateral reactive hydrocele was detected in 16 (76.2%) patients. Doppler US showed decreased and/or absent ipsilateral testicular blood flow in all patients.

While 4 of 21 patients underwent intraoperative orchiectomy, operative detorsion was performed in 17 patients. Testicular atrophy was detected within the postoperative first year in three patients out of 17 patients treated with operative detorsion. Orchiectomy was performed for these three atrophic testes.

We have summarized serum IMA levels of the patients in Table 2. The serum IMA levels of patients who underwent operation due to TT were statistically significantly higher compared with the control group [34.50 (22.65-61.45) and 13.50 (6.10-24.30); respectively] ($p<0.001$). No statistical difference was detected between the serum IMA levels of intraoperative orchiectomy and testicular atrophy after detorsion groups (p=0.857). Serum IMA levels of intraoperative orchiectomy and testicular atrophy after detorsion groups were significantly higher compared with no testicular atrophy after detorsion group (p=0.013 and p=0.012, respectively).

ROC curve analyses of IMA were also performed. ROC analysis revealed an optimal cut-off point at 18.90 ng/mL for separating the TT group (n=21) from the control group (n=31). The sensitivity and specificity were 90.5% and 61.3%, respectively. The area under the curve for IMA was 0.885 ($p<0.001$). And also, ROC analysis revealed an optimal

Table 1. Clinical features of TT patients

	n (%)
Scrotal pain scrotal pain	20 (95.2)
Nausea and/or vomiting	7 (33.3)
Scrotal hyperemia	15 (71.4)
Scrotal swelling and edema	17 (81.0)
Absence of cremasteric reflex	17 (81.0)

TT: Testicular torsion

Table 2. Serum IMA levels of the patients

Groups	IMA levels (ng/mL)
Control (n=31)	13.50 (6.10- 24.30)*
TT requiring orchiectomy (n=4)	69.30 (55.25-82.97)†
No testicular atrophy after operative detorsion (n=14)	25.20 (20.90-35.15)
Testicular atrophy after operative detorsion (n=3)	66.40 (50.30-66.40)‡

Data presented as median and interquartile range
*: Control group compared with TT requiring orchiectomy, no testicular atrophy after detorsion and testicular atrophy after detorsion groups ($p<0.001$), †: TT requiring orchiectomy group compared with no testicular atrophy after detorsion group (p=0.013), ‡: Testicular atrophy after detorsion group compared with no testicular atrophy after detorsion group (p=0.012), TT: Testicular torsion

Table 3. Duration of symptom and torsion degrees of the patients

Groups	Duration of symptom (hours)	Torsion degrees
TT requiring orchiectomy (n=4)	72.00 (54.00-108.00)	630 (540-720)†
No testicular atrophy after operative detorsion (n=14)	6.30 (5.75-14.75)*	360 (360-540)
Testicular atrophy after operative detorsion (n=3)	36.00 (24.00-60.00)	360 (360-600)

Data presented as median and interquartile range, *: No testicular atrophy after detorsion group compared with TT requiring orchiectomy and testicular atrophy after detorsion groups (p=0.004 and p=0.006),
†: TT requiring orchiectomy group compared with no testicular atrophy after detorsion group (p=0.008),
TT: Testicular torsion

cut-off point at 43.70 ng/mL for separating TT with orchiectomy (n=7) from TT without orchiectomy (n=14). The sensitivity and specificity were 100.0% and 85.7%, respectively (the area under the curve was 0.959, p=0.001).

Duration of symptoms was notably prolonged in both TT requiring intraoperative orchiectomy group and testicular atrophy after detorsion group compared with no testicular atrophy after detorsion group (p=0.001 and p=0.006, respectively) (Table 3). There was a positive correlation between IMA values and the duration of symptoms (r=0.744, p<0.001) but we couldn't find any association between the clinical features of TT patients and IMA values (p>0.05). Degree of TT was more in intraoperative orchiectomy group compared with detorsion groups (p=0.008) (Table 3).

According to the duration from admission to surgery, there was no difference between TT requiring orchiectomy [30.0 min (22.5-30.0 min)], no testicular atrophy after operative detorsion [35.0 min (30.0-42.5 min)] and testicular atrophy after operative detorsion [40.0 min (30.0-40.0 min)] (p=0.195). The median duration of operation was 60 minutes (47.5-75.0 minutes). Postoperative scrotal hematoma developed in three patients and resolved during follow-up without need for any intervention.

Discussion

Twisting of the spermatic cord along the longitudinal axis, causes obstruction of blood vessels supplying the testis. Severity of blood flow obstruction directly correlates with the degree of ischemic testicular injury, possible functional loss of testis and infertility. One of the notable debates in TT, which can lead to serious consequences, is the decision making for intraoperative orchiectomy.[13] In the literature, 6-hour cut-off value is widely used to define early and late presentations for TT. Saxena et al.[14] showed that intraoperative orchiectomy rate in TT increased from 9.1% to 56% after the 6-hour mark. Similarly, Bayne et al.[15] reported that the most important factor affecting intraoperative orchiectomy rate in TT was time from onset of symptoms to patient presentation. They emphasized that 76.7% of the TT patients presenting 24 hours after onset of symptoms underwent intraoperative orchiectomy as opposed to 10% of patients presenting with in the first 6 hours after onset of symptoms. Duration of symptoms stands out as an important parameter during decision making for intraoperative orchiectomy. Another important parameter in terms of testicular viability is the degree of TT. Castañeda-Sánchez et al.[16] reported that testicular damage increases as the degree of TT increases. The degree of TT was more in patients who underwent intraoperative orchiectomy compared with patients who underwent operative detorsion. In the present study, duration of symptoms was statistically significantly longer in patients who underwent intraoperative orchiectomy and in patients who developed atrophy after operative detorsion. However, duration of symptoms seemed important predicting surgical outcomes, factors such as torsion degree and torsion type may also have an impact. The need to objectively and measurably evaluate the severity of testicular ischemia, which is the common result of all these factors, still continues.

Overall, 38% of TT has been shown to result in intraoperative orchiectomy.[17,18] Several experimental and clinical studies investigated the value of different biochemical parameters in assessing permanent testicular damage after TT.[4-6,10-12,19] One of the markers that can be used for this purpose is IMA. IMA is a sensitive marker that increases with ischemia and oxidative stress.[7,12] Testicular tissue is highly sensitive to oxidative free radicals and exposure to oxidative free radicals damages the germinal cells.[20] Experimental studies shown that serum IMA levels increase after TT.[10-12] Kutlu et al.[12] experimentally showed that serum IMA levels were increased after the 4th hour of TT. They reported that although no significant correlation between histopathologic damage and serum IMA levels, significantly high histopathologic damage in present 4 hour torsion group. Although this study does not evaluate IMA values over 4 hours, it is also valuable in that it shows the increase in IMA values as the duration of symptoms increases. They also suggested that IMA is the potential diagnostic value for TT and that IMA levels in TT should be investigated concerning prognosis. Kutluhan et al.[11] experimentally showed that low serum IMA levels in the early hours of TT may indicate preservation of high spermatogenesis capacity.[11] Mentese et al. [21] has shown that the elevation in serum IMA levels persists for as long as experimental testicular ischemia continues. To the best of our knowledge, there is no clinical

study in the literature regarding the usefulness of serum IMA in patients operated for TT. In our study, the IMA value increased and was positively correlated with ischemia and symptom duration. It was found that an IMA value of 18.90 ng/mL (90.5% sensitivity, 61.3% specificity) helped in the diagnosis of TT. When this value was taken as 43.70 ng/mL (100% sensitivity, 85.7% specificity), it served as a prognostic indicator.

The main controversies in TT are which patients will undergo intraoperative orchiectomy and whether testicular viability be predicted in the postoperative period. Considering the aforementioned discussions, it is obvious that intraoperative orchiectomy or operative detorsion will have vital effects on the ipsilateral testis and therefore on a child's reproductive capacity. We conducted a prospective case-controlled study on the value of serum IMA levels on the decision making for intraoperative orchiectomy and during predicting postoperative testicular atrophy after operative detorsion. As a result of our study, IMA was shown to be a useful parameter in terms of indicating testicular ischemia and testicular atrophy which may develop in the future, consistent with our findings. The present study has shown that, serum IMA values in cases who underwent intraoperative orchiectomy were found to be statistically significantly higher compared with control and no testicular atrophy after detorsion groups. Serum IMA values of patients who developed testicular atrophy after operative detorsion were statistically significantly higher compared to those of the control group and the no testicular atrophy group after operative detorsion. Serum IMA levels of the patients who underwent intraoperative orchiectomy and those of patients who developed testicular atrophy after detorsion were similar. Intraoperative visual evaluation of testicular blood flow is subjective. Serum IMA levels may be used in decision-making during intraoperative orchiectomy and in predicting testicular atrophy after operative detorsion.

Conduction of the present study in a single center and on limited number of patients was the main limitations that may limit the generalization of the results. Another limitation is that serum IMA does increase in several other ischemic conditions other than TT.

Conclusion

IMA has become a prominent biomarker in recent years regarding the role of ischemia in several diseases and studies are currently ongoing. In the present clinical study, we found that serum IMA levels are a valuable biomarker for the diagnosis of childhood TT, in predicting testicular atrophy, and therefore, deciding on intraoperative orchiectomy.

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Non-Interventional Research Ethical Committee (decision no: 2022/03-11, date: 19.01.2022).

Informed Consent: Informed consent was obtained from parents or legal guardians before enrollment in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.U., A.B., E.U., Concept: O.U., M.Ş., A.B., E.U., Design: O.U., M.Ş., E.U., Data Collecting or Processing: O.U., A.B., E.U., T.K., Analysis or Interpretation: O.U., E.U., O.A., G.H., M.O., M.F.A., Literature Search: O.U., E.U., O.A., G.H., M.O., M.F.A., Writing: O.U., E.U., O.A., G.H., M.O., M.F.A.

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