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Can Surgical Technique Affect the Success of Endoscopic Treatment in Children with Vesicoureteral Reflux and Overactive Bladder Syndrome?

Vezikoüreteral Reflü ve Aşırı Aktif Mesane Birlikteliğinde Farklı Endoskopik Cerrahi Teknikler Tedavi Başarısını Etkiler mi?

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What's known on the subject? and What does the study add?

The surgical correction of vesicouretral reflux in children with concomitant overactive bladder is a challenging issue in pediatric urology practice. While no significant difference exists between the success rates of the STING and Double-HIT treatment methods, the presence of high-grade reflux is a parameter that can be used to predict the success of the treatment in patient with concomitant overactive bladder.

ABSTRACT

Objective

"Traditional subureteral transurethral injection" (STING) and "Double hydrodistention-implantation" (Double-HIT) injection techniques for vesicoureteral reflux (VUR) treatment are a less invasive, yet very effective options. The influence of injection techniques in treatment success is not adequately searched in children with overactive bladder syndrome (OAB). The objective of this study to compare the short-term success rates of STING and Double-HIT techniques in children with OAB-VUR complex.

Materials and Methods

Children who underwent endoscopic injection for VUR between 2010 and 2013 were retrospectively evaluated. Patients were grouped into two groups according to the surgical techniques (STING or Double-HIT). Success of the treatment was defined with a negative voiding cystourethrogram at the 6th postoperative week. Patients were evaluated according to sex, age, pre- and postoperative reflux grades, laterality, type and volume of bulking agent and presence of OAB.

Results

Both groups were similar in terms of sex, age, lower urinary tract dysfunction, reflux grade and success rates. Surgical technique, score of pediatric lower urinary tract symptom questionnaire, age, sex, laterality of reflux and type of the bulking agent found to have no effect on the overall success rates (p>0.05). Presence of OAB and/or a high grade reflux were identified as statistically significant predictive factors that could affect the treatment results.

ÖZET

Amaç

Vezikoüreteral reflü (VUR) tedavisi için kullanılan cerrahi yöntemlerden subüreteral transüretral enjeksiyon (STING) ve çift hidrodistansiyon-implantasyon (Double-HIT) enjeksiyon teknikleri daha az invazif ve etkili tedavi seçenekleridir. Aşırı aktif mesane (AAM) ve VUR birlikteliği olan çocukların tedavilerinde enjeksiyon tekniklerinin etkisi henüz yeterince araştırılmamıştır. Bu çalışmanın amacı AAM-VUR birlikteliği olan çocukların tedavisinde STING ve Double-HIT tekniklerinin kısa süreli başarı oranlarının karşılaştırılmasıdır.

Gereç ve Yöntem

Kliniğimizde 2010-2013 yılları arasında VUR tedavisi için endoskopik enjeksiyon yapılan çocuklar retrospektif olarak değerlendirildi. Çocuklar kullanılan cerrahi tekniğe göre (STING veya Double-HIT) iki gruba ayrıldı. Tedavinin başarısı postoperatif 6. haftadaki işeme sistoüretrogramında (İSUG) reflünün tamamen kaybolması olarak tanımlandı. Hastalar cinsiyet, yaş, preoperatif ve postoperatif reflü derecesi, tek-çift taraf, enjeksiyon materyali tipi ile hacmine ve AAM varlığına göre değerlendirildi.

Bulgular

Her iki grup cinsiyet, yaş, alt üriner sistem disfonksiyonu ve reflü derecesi varlığı açısından benzerdi. Kullanılan cerrahi tekniğin, pediatrik alt üriner sistem semptomları anket skorunun, yaşın, cinsiyetin, reflü tarafının ve enjeksiyon materyalinin türünün; genel başarı oranları (p>0,05) üzerine anlamlı bir etkisi yoktu. Yüksek dereceli VUR tedavisinde AAM'nin varlığı tedavi başarısını öngörmede istatistiksel olarak anlamlı bir faktör olarak bulundu.

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ABSTRACT

Conclusion

The short-term surgical success of the double-HIT and STING techniques showed no difference in children with OAB. The presence of a high grade reflux and/or OAB seemed to be the main factors for overall success in endoscopic VUR surgery.

Key Words

Pediatrics, vesicoureteral reflux, overactive bladder, endoscopic surgery, surgery, therapy

ÖZET

Sonuç

Double-HIT veya STING tekniği kullanarak tedavi edilen AAM'li çocuklarda kısa süreli cerrahi başarı oranları önemli bir fark göstermemektedir. Yüksek dereceli VUR ve/veya AAM varlığı endoskopik VUR cerrahisi başarısını veya başarısızlığını belirleyen temel faktörler olarak görülmektedir.

Anahtar Kelimeler

Pediatri, vezikoüreteral reflü, aşırı aktif mesane, endoskopik cerrahi, tedavi, cerrahi

Introduction

Endoscopic injection treatment for vesicoureteral reflux (VUR) is a less invasive, yet very effective surgical option. Following the commercial release of dextranomer/hyaluronic acid copolymer (Dx/HA) material, it has became increasingly common with success rates of 83.0% (95% CI, 69.1-91.4%) following the first injection (1). Not long ago, Kirsch et al. (2) offered an alternative technique for the traditional subureteral transurethral injection (STING) method and with their new technique, they report higher cure rates in endoscopic vesicoureteral reflux (VUR) surgery which evolved from 79% up to 92%. This new form of STING application suggests intraureteral injection of Dx/HA and is thought to provide a better coaptation (2). This technique of Kirsh, hydrodistention implantation technique (HIT), was further modified into another one with the injection of Dx/HA both into the ureter and into the ureteral orifice (double-HIT) by Molitierno et al. (3) and Kalisvaart et al. (4). In their original work, they reported better results, with a success rate of 92-93% for double-HIT technique. This two-step technique provides a sufficient bulge and a coaptation of the detrusor tunnel and helps ureteral orifice to have a better coaptation, respectively (5). In both injection techniques, an optimal bolus and slit-like ureteral orifice appearance has been reported (6). Migration of the bulking agent, insufficient injection, inappropriate localization for injection, extrusion of the implant, and multiple mucosal ruptures are the proposed failure reasons for STING (5). Predictive factors for treatment success include pre/post-operative ureteral orifice morphology, grade of preoperative reflux, appropriate injection volume and presence of lower urinary tract dysfunction (LUTD) (5,7,8). More recent studies report similar success rates for HIT, double-HIT and STING techniques in contrast to former literature, which suggests double-HIT method as being more effective (3,4,9,10). According to 2010 AUA guidelines, the rate of reflux resolution at the 24th month after diagnosis is much lower for children with LUTD (31%) than it is for children without it (61%) (1). The rate of cure following endoscopic therapy is less in children with than it is for children without LUTD, but there is no difference in the case of open surgery (1,11,12). The influence of injection techniques on treatment success is not adequately searched in children with overactive bladder (OAB). The present study aims to assess results and success rates of both injection techniques in children with VUR and OAB complex.

Materials and Methods

Patients and Diagnosis of Reflux

Previously detected VUR patients, who underwent an endoscopic injection treatment between February 2010 and February 2013, were enrolled into the present study. Each child's age, gender, pediatric lower urinary tract symptom score (PLUTSS), two-day voiding dairy data, constipation history, genital and sacral examinations, uroflow/EMG study, urinary ultrasonography, voiding cystouretrography (VCUG), and dimercaptosuccinicacid sintigraphy (DMSA) results were recorded. This study was approved by the Local Ethics Committee and conducted in accordance with the ethical principles described by the Declaration of Helsinki (ID: 09.2014.0121).

Diagnosis and Treatment of OAB

Patients who met the following three criteria were classified as suffering from OAB and were selected as the study group: (1) sudden, imperative urinary urgency with or without urge incontinence; (2) need for holding maneuvers; (3) a minimum of seven small-volume urinations per day. Findings that supported the diagnosis of OAB were normal or low bladder capacity and a post-void residual urine volume of <20 mL (7). Each patient and his/her parents completed a originally developed and validated score (PLUTSS) for lower urinary tract symptoms at the initial evaluation phase and 6 months thereafter (13).

Each patient completed a 2-day bladder diary with entries as per International Children's Continence Society (ICCS) recommendations (7).

Patients with OAB were treated with anticholinergics (0.1-0.3 mg/kg) and urotherapy for minimum 6 months. Finally, patients with persisting reflux were included in the study. Children having complex VUR, a history of previous reflux surgery, neurogenic bladder, duplicated ureter, ectopic ureter, or posterior urethral valve were excluded from the study. VUR diagnoses and grading was carried out according to the International Reflux Study Criteria (14). Recurrent febrile urinary tract infections despite appropriate antibiotic prophylaxis, presence of newly diagnosed renal scarring, persisting or worsening of VUR following OAB treatment and family will were the main indications for endoscopic VUR surgery.

Surgical Technique

Operations were performed under general anesthesia with 0-5 degree lens through a 10.5 Fr pediatric cystoscope. Any endoscopic treatment needs the placement of cystoscope at the ureteral orifice and placing the irrigation bag approximately 1 meter above the bladder on full flow for hydrodistention of the intramural ureter and a fine pressure stream.

STING procedure involves placement of the needle just in front of the ureteral orifice at a 6 o'clock position and introduction of the needle to the depth of 2-3 mm of bladder mucosa (6). The injection is

continued until a satisfactory bulge and a good shut tight coaptation is gained at the ureteral orifice, like a volcano (6).

Double-HIT involves placement of the needle to the mid-ureteral tunnel and injection of bulking agent at the 6 o`clock position after a prior injection of the implant under the intramural ureter; thus, preventing the risk of displacement of the implant and providing a better ureteral tunnel coaptation (5,15). Dx/HA implant materials used for injections were either DEXELL VUR® (80-120 microns; Elit Medikal, Ankara-TURKEY) or DEFLUX® (80-250 micron; Oceana Therapeutics Ltd., Dublin-IRELAND). For evaluation of surgical success, an ultrasound and VCUG imaging were performed at 6th postoperative week for Dexell and 3 months for Deflux. We monitored initially reflux-free patients for febrile urinary tract infection (UTI), VUR relapse and voiding dysfunction (VD) presence, laterality, need for control VCUG and time to relapse.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp.) Chi-square and Fisher's exact tests were used where appropriate. The univariate analyses were done by using the chi-square, Fisher's exact, student's t-test, and the Mann-Whitney U tests where appropriate. In multivariate analyses, logistic regression analyses were done to determine independent predictors. Tests were considered statistically significant when p values were less than 0.05.

Results

Of all patients, 82 children received a subureteric injection via STING technique and 31 received via double-HIT injection technique. Both groups were similar in terms of sex, age, PLUTSS, reflux laterality, preoperative reflux grade and success rates (p>0.05) (Table 1). Demographic findings in each group are provided in Table 1.

Surgical technique was found to have no statistically significant effect on success/failure rates when compared in a subgroup analysis according to reflux grade, treated ureteral unit, treated patient number and presence of OAB (Table 2) (p>0.05). In univariate analysis, treatment efficacy was found to be influenced by age, PLUTSS, accompanying OAB, and preoperative reflux grade (Table 3) (p<0.05). On the other hand, sex, reflux laterality, type of bulking agent, and surgical technique had no influence on treatment success (Table 3) (p>0.05).

Binary logistic regression analyses of surgical technique, presence of OAB, presence of a high reflux grade, PLUTSS and age revealed significant effect of accompanying OAB and high grade reflux on treatment success (Table 4).

During the long-term follow-up, 13 (15.8%) of the 82 initially reflux-free patients developed febrile UTI and underwent VCUG. Seven (8%) of them had recurrences. Three ipsilateral and 4 new contralateral VUR were documented. Lower urinary tract symptoms were reported in 4 of 13 patients. Two of them developed contralateral VUR and

Table 1. Descriptive statistics of the study groups are given

		Double HIT	STING	p value
Sex	Male	1 (6.7%)	14 (93.3%)	0.06*
	Female	30 (30.6%)	68 (69.4%)	
Age by years (Mean ± SD)		7.8±2.6 years	7.3±3.3 years	0.42$^{\infty}$
PLUTSS (Mean ± SD)		9.6±8.2	11.8±5.5	0.14$^{\mu}$
Dx/HA volume by ml (Mean ± SD)		1.37±0.35 ml	1.25±0.54 ml	0.286$^{\beta}$
Laterality	Unilateral	23 (74.2%)	52 (63.4%)	0.375*
	Bilateral	8 (25.8%)	30 (36.6%)	
Age	<5 years	4 (12.9%)	17 (20.7%)	0.177*
	≥years	27 (87.0%)	65 (79.3%)	
LUTD	OAB	13 (41.9%)	41 (50%)	0.444*
	Normal	18 (58.1%)	41 (50%)	
Dx/HA material	DEFLUX®	0 (0%)	76 (100%)	0.001
	DEXELL® VUR	62 (41.3%)	88 (58.7%)	
VUR grade	1	6 (9.7%)	9 (5.5%)	0.154*
	2	21 (33.9%)	46 (28.0%)	
	3	10 (16.1%)	35 (21.3%)	
	4	2 (3.2%)	21 (12.8%)	

*Chi-square test, $^{\infty}$Student t test, μ Mann Whitney-U test, $^{\beta}$Student t test, SD: Standard deviation, Dx/HA: Dextranomer/hyaluronic acid copolymer, OAB: Overactive bladder, PLUTSS: Pediatric lower urinary tract symptom score, LUTD: Lower urinary tract dysfunction, STING: Traditional subureteral transurethral injection, VUR: Vesicoureteral reflux, Double HIT: Double hydrodistention-implantation

Table 2. Treatment results of subureteric injection techniques are compared

Treatment results (According to reflux grade)		Double HIT	STING	Total	p value
	Grade 1	4/6 (66.7%)	9/9 (100%)	13/15 (86.7%)	0.143∞
	Grade 2	18/21 (85.7%)	39/46 (84.8%)	58/67 (85.1%)	0.921β
	Grade 3	7/10 (70%)	27/35 (77.1%)	34/45 (75.6%)	0.687∞
	Grade 4	0/2 (0%)	11/21 (52.4%)	11/23 (47.8%)	0.478
Ureteral unit		29/39 (74.4%)	86/111 (77.5%)	117/150 (76.6%)	0.692β
Patient number		22/31 (71.0%)	61/82 (74.4%)	83/113 (73.4%)	0.713β
LUTD	OAB	10/17 (58.8%)	34/54 (63.0%)	44/71 (61.9%)	0.759β
	Normal	19/22 (86.4%)	52/57 (91.2%)	81/101 (80.1%)	0.679β

∞(fisher's exact test), β(Chi-square),
LUTD: Lower urinary tract dysfunction, STING: Traditional subureteral transurethral injection, Double HIT: Double hydrodistention-implantation,
LUTD: Lower urinary tract dysfunction, OAB: Overactive bladder

Table 3. Treatment success is compared according to various variables with univariate analysis

		Treatment success (n=115)	Treatment failure (n=35)	p value
Sex	Female	97 (77.0%)	29 (23.0%)	0.833*
	Male	18 (75.0%)	6 (25.0%)	
Age by years (Mean ± SD)	Total	7.6±3.3	6.3±3.0	0.03β
PLUTSS (Mean ± SD)		10.5±6.3	14.7±-6.3	0.01β
Age	<5 years	20 (62.5%)	12 (37.5%)	0.033*
	≥. years	95 (%80.5%)	23 (19.5%)	
OAB (Total 28)	Yes	44 (62.0%)	27 (38.0%)	0.001*
	No	71 (89.9%)	8 (10.1%)	
Preoperative reflux grade	Grade 1	13 (86.7%)	2 (13.3%)	0.003*
	Grade 2	57 (85.1%)	10 (14.9%)	
	Grade 3	34 (75.6%)	11 (24.4%)	
	Grade 4	11 (47.8%)	12 (52.2%)	
Dx/HA volume (Mean, min-max)		1.30 (0.5-2.0)	1.23 (1.0-2.0)	0.353∞
Laterality	Unilateral	27 (87.1%)	4 (12.9%)	0.233*
	Bilateral	28 (75.7%)	9 (24.3%)	
Bulking agent	DEFLUX®	39 (76.5%)	12 (23.5%)	0.967*
	DEXELL VUR®	76 (76.8%)	23 (23.2%)	
Injection technique (For all Dx/HA materials)	STING	86 (74.4%)	25 (25.6%)	0.692*
	Double HIT	29 (77.5%)	10 (22.5%)	
Injection technique (For only DEXELL VUR®)	STING	47 (78.3%)	13 (21.7%)	0.647*
	Double HIT	29 (74.4%)	10 (25.6%)	

*Chi-square, βstudent t test, ∞ Mann-Whitney U test, SD: Standard deviation, Dx/HA: Dextranomer/hyaluronic acid copolymer, OAB: Overactive bladder, PLUTSS: Pediatric lower urinary tract symptom score, VUR: Vesicoureteral reflux

Table 4. Binary logistic regression analyses of variables that might have an effect on treatment success are provided with confidence interval

	Sig.	Exp (B)	95% C.I. for Exp (B)	
			Lower	Upper
OAB vs. Normal function	.036	3.375	1.085	10.498
Reflux (Grade 1-2 vs. Grade 3-4)	.028	2.996	1.123	7.993
Reflux (Grade 1-2-3 vs. Grade 4)	.008	4.391	1.473	13.087
Double HIT vs. STING	.267	1.737	0.655	4.606
PLUTSS	.175	.944	0.869	1.026
Age	.282	1.087	0.934	1.265

OAB: Overactive Bladder, PLUTSS: Pediatric lower urinary tract symptom score, STING: Traditional subureteral transurethral injection, Double HIT: Double hydrodistention-implantation

one of them had ipsilateral VUR. Four of 7 patients with recurrence underwent subureteric injection via STING technique and the rest 3 received via double-HIT injection technique. The mean reflux recurrence time was 16 months.

Discussion

The present study retrospectively analyzed the effect of age, sex, the type and amount of injected agent, laterality, reflux grade, PLUTSS and presence of OAB in endoscopic treatment of VUR. Finally, we found that being younger (<5 years), having a low PLUTSS, having a reflux of low grade, and being without OAB seemed to increase the success of endoscopic VUR treatment. According to regression logistic analyses, reflux grade and accompanying OAB seemed to be the ultimate factors determining overall success of endoscopic surgery.

Similar to the present study, a meta-analysis covering 17.972 patients reported high success rates for VUR treatment via endoscopic treatment and open surgery as 83% and 98.1%, respectively (1). Interestingly, our success rate for endoscopic treatment of VUR was slightly low (76.7%) compared to the meta-analysis. Some authors think endoscopic treatment can even be spared for high-grade reflux. Altug et al. (15) reported a 54.8% cure rate for grade 3-4-5 reflux after first injection treatment. However, most of the endoscopic treatments in grade 5 reflux patients were reported as failed, so the actual cure rates for grade 3-4 reflux appeared to be much higher as 66.1%. We do not think that endoscopic treatment is the right treatment modality for a VUR with grade 5, and our cure rates for grade 3-4 and grade 4 were 66.2% and 48.7%, respectively.

Watters et al. (9) reported ureteral reflux resolution as 79.75% and 80.84% for STING and HIT techniques, respectively (p=0.86). On the other hand, Yucel et al. (8) reported successful reflux resolution in 124 ureters (84%) with a single implantation, including 83 (86.5%) with double-HIT and 41 (79%) with HIT techniques (p=0.23). Similarly, we could not find any statistically significant difference between either techniques (74.4% vs. 77.5%). However, a debate about this topic still goes on since some of the recent studies, like the one performed by Routh et al.(16) reported double-HIT technique being more effective although this did not achieve statistical significance. Watters et al. (9) could not find any effect of injection technique, patients' sex, presence of VD, and orifice morphology on success rate (OR=4.4, p=0.004), but they found two significant predictors of treatment success which were being younger than 6 years and using moderated amount of Dx/HA volume (OR=2.7, p=0.003) (9). We also have a similar experience with age. Since toilet training is generally expected to be gained at age 5, we preferred to analyze patients prior or after age 5; talking about our cohort patients younger than 5 years old seemed to have a higher failure rate (37.5% vs. 19.5%).

Several case studies have been published reporting various causes affecting surgical success rates like the injection method used, preoperative reflux grade, pre/post-operative ureter orifice morphology, amount of injected Dx/HA, and associated any lower urinary tract dysfunction (8,17,18). Lavelle et al. (18) reported postoperative ureter orifice morphology to be the main factor of success. Unlike us, they did not perform urodynamic studies and did not use any questionnaire in the evaluation of VD, and did not find VD and reflux grade to be the predictive factors. Mendez et al. (16) investigated the effect of laterality of reflux and presence of either VD or nephropathy; and found only reflux grade to be a significant predictor of treatment success. Yucel et al. (8) determined preoperative reflux grade (OR=0.46, p<0.001), amount of injected material (OR=0.3, p=0.046), and post-operative orifice morphology (OR=11.5, p=0.001) as the most important factors influencing surgical success. The injection technique used, on the other hand, was reported as not being influential in surgical success. We could not show the effect of volume for injected material on surgical success (1.30 ml vs. 1.23 ml). Kessler studied patients with reimplantation surgery after primary injection failure and found VD as the primary factor influencing cure rates among factors, such as ureter orifice morphology, in addition to other factors, such as preoperative reflux grade, presence of VD, injected material amount and injection method (19). In order to suggest any effect of orifice morphology on surgical success, investigators must ask several urologists about the pre/post-operative orifice view for exclusion of inter-observational bias. We did not evaluate the ureteral orifice morphology as Kessler and Yucel have reported (19). Ural et al. (11) reported overall resolution rates in children with reflux and accompanying VD as 58%, 71%, 26% and 21% for reflux grades 1 through 4, respectively and suggested that high filling pressure might be a cause of reflux in this group of patients. Resolution rates of reflux in the present study was found to be 75%, 77.4%, 54.5% and 35.7%, for each grade, respectively.

Stredele at al. (2) reported that 81.5% of the ureters were without VUR after the first Dx/Ha injection at three months postoperatively and, during long-term follow-up at 3 years, 21.5% of the initially VUR-free ureters relapsed, showing VUR again on the (nuclide) VCUG. Forty-one of 62 patients were without any complication since the Dx/Ha injection. Ten of the remaining 21 patients developed less than 2, while 11 patients developed more than 2 times non-febrile UTI. None of them developed febrile UTI. In our report, out of 82 patients, 13 (15.8%) who were compliant with UTI (febrile or afebrile) underwent VCUG. Seven of 13 patients had VUR (8%). We included also patients with grade 1 VUR in our study unlike Stredele's report (2). Despite exclusion of patients having grade 1 reflux in our study, only 15 patients (11.8%) developed relapse VUR. However, our study report covered only clinical follow-up results and shorter follow-up time (16 months vs. 24 months) when compared with the previously described

study. There was still a risk of VUR recurrence in successfully treated children after 3 years of follow-up.

The present study is consistent with the previously published literature, except one setting; it included only patients with OAB. No serious averse events were confronted in the present study. In a sub-group analysis, the success rates got slightly higher up to 61.9% (44/71) as the patients with known neurogenic bladder and other VD were excluded.

There are several limitations in our study. As this is a retrospective study evaluating the short-term findings in a limited number of patient operated by more than one surgeon, it might have inherent biases and false success rates, and might be underpowered to compare factors known to impact the natural history of VUR resolution in a long-term period. A prospective-randomized study with a larger number of patients should be pursued to overcome these limitations.

Conclusion

Short-term evaluation of OAB-VUR complex patients showed similar success rates for both forms of endoscopic anti-reflux surgery techniques, namely for STING and double-HIT. Grade of reflux and presence of VD appears to be the most important factors affecting the success rates in endoscopic anti-reflux surgery in OAB-VUR complex patients.

Ethical Standards

All patients' parents gave their informed consent prior to their treatment in our academic center. Details that might disclose the identity of the subjects under the present study are omitted.

Ethics Committee Approval: The study were approved by the Marmara University of Local Ethics Committee (ID: 09.2014.0121), **Informed Consent:** Consent form was filled out by all participants, **Concept:** Cem Akbal, Tufan Tarcan, Ferruh Şimşek, **Design:** Cem Akbal, Tufan Tarcan, Ferruh Şimşek, **Data Collection or Processing:** Asgar Garayev, Çağrı Akın Şekerci, Muhammed Sulukaya, İlker Tinay, **Analysis or Interpretation:** Ahmet Şahan, Yılören Tanıdır, **Literature Search:** Ahmet Şahan, Asgar Garayev, İlker Tinay, **Writing:** Ahmet Şahan, Cem Akbal, **Peer-review:** Externally peer-reviewed, **Conflict of Interest:** No conflict of interest was declared by the authors, **Financial Disclosure:** The authors declared that this study has received no financial support.

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