

Comparison of the clinical characteristics of patients with varicocele according to the presence or absence of scrotal pain

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Abstract

We investigated the clinical characteristics of patients with varicocele according to the presence or absence of scrotal pain. We retrospectively reviewed the records of patients who underwent varicocelectomy. The age, body mass index, grade, laterality of varicocele, testicular volume difference, time to hospital visit, serum testosterone level and semen parameters were evaluated. A total of 954 patients were included. The painful group had lower mean age, lower BMI, higher grade of varicocele, smaller testicular volume difference and shorter time to hospital visit than the painless group. In addition, the median serum total testosterone level and total sperm count, concentration and motility were higher in the painful group than in the painless group. In multivariate analysis, there were significant differences between the two groups in age, grade of varicocele, testis volume difference, time to hospital visit, total sperm count and concentration. Patients with painful varicocele visited hospital earlier because of the pain and tended to start treatment sooner. They were also younger, had smaller testis atrophy and had higher sperm concentration, even though they had a higher grade of varicocele than patients without pain. Although scrotal pain in varicocele patients is difficult to treat, it leads to early diagnosis and treatment.

KEYWORDS

pain, scrotum, testis, varicocele

1 | INTRODUCTION

Scrotal pain is not a symptom in all patients with varicocele. It is seen in only some patients and is characterised by intermittent occurrence (Owen, McCormick, Figler, & Coward, 2017; Tan & Levine, 2017). However, varicocele-induced scrotal pain does not respond well to medication, and some patients have pain after surgery (Park, Lee, & Park, 2011). Consequently, physicians find it difficult to manage patients with painful varicocele (Tan & Levine, 2016, 2017).

The first step in the management of painful varicocele is to distinguish varicocele-induced pain from the various other causes of scrotal pain. Diseases that can cause scrotal pain include tumour,

torsion, varicocele, hydrocele, spermatocele, inguinal hernia, epididymo-orchitis and stones (Tan & Levine, 2017). After an accurate diagnosis confirms that the scrotal pain is caused by a varicocele, initial conservative management is recommended, including limitation of physical activities, scrotal elevation and treatment with nonsteroidal, anti-inflammatory analgesics before surgery. However, these often do not result in successful pain management (Park et al., 2011). Varicocelectomy is an alternative treatment for patients with painful varicocele who do not show enough improvement after conservative management (Lundy & Sabanegh, 2018). Because varicocele is not a disease that can be cured by medication, it is difficult to predict the effect of medical treatment for scrotal pain confirmed to be induced

by varicocele. Therefore, varicocelectomy should be considered, but guidelines have focused on the surgical indication for varicocele as it relates to infertility (Dohle et al., 2005; Roque & Esteves, 2016). Nevertheless, many studies have investigated the efficacy of surgical treatment of painful varicocele and reported various therapeutic outcomes. However, not all studies consistently show satisfactory surgical results (Elzanaty & Johansen, 2015; Karademir et al., 2005; Maghraby, 2002; Park et al., 2011; Schlegel & Goldstein, 2011). On the other hand, many studies have revealed the characteristics of patients with painful varicocele who show satisfactory outcomes after surgical treatment (Altunoluk, Soylemez, Efe, & Malkoc, 2010; Elzanaty & Johansen, 2015; Kim, Song, & Moon, 2012; Park et al., 2011). This means that appropriate patient selection is important for the successful treatment of painful varicocele. The main reasons patients with painless varicocele present to their physician include lumps in the scrotum and fertility problems. Therefore, diagnosis of varicocele in patients without scrotal pain is often delayed. In other words, the presence of pain can cause discomfort to the patient but can increase the likelihood of an early diagnosis of varicocele, a condition that may impair future fertility. We postulated that if the duration of varicocele before treatment varies depending on the presence of pain, it might be associated with significant parameters, including sperm quality in patients with varicocele.

With this background, we investigated the clinical characteristics of patients with varicocele according to the presence or absence of scrotal pain.

2 | MATERIALS AND METHODS

2.1 | Subjects

We retrospectively reviewed the records of patients who underwent varicocelectomy in a single centre from 1997 to 2016. Patients who received varicocelectomy were divided into those with scrotal pain and those without pain. Scrotal pain was defined as continuous or intermittent discomfort or pain of any of the organs in the scrotum forcing the patient to seek medical assistance. Patients who had other causes of scrotal pain, such as epididymitis, orchitis, sexually transmitted disease, urinary tract infection, urolithiasis, prostatitis, inguinal hernia, testicular torsion, testicular tumour or trauma or a history of inguinal surgery, were excluded from the study.

2.2 | Methods

To investigate the clinical characteristics according to the presence or absence of pain between the two groups, the parameters to be investigated were selected for comparison. The parameters included age, body mass index (BMI), grade and laterality of varicocele, testis volume difference, time to hospital visit, serum total testosterone level and semen analysis. We compared each parameter in both groups. In addition, patients in each group were subdivided by parameters for comparison: age at surgery (<18 or ≥18 years), BMI

(<18.5, 18.5–22.9, 23–24.9, or ≥25.0 kg/m²), location (left, right, or bilateral), grade of the varicocele, time to visit hospital (<6, 6–12, or >12 months), testicular volume difference (<1, 1–3, or >3 ml) and serum total testosterone level (<350 or ≥350 ng/dl). The varicocele was graded according to criteria defined by Lyon, Marshall, and Scott (1982): grade I, palpable only with the Valsalva manoeuvre; grade II, palpable without the Valsalva manoeuvre; and grade III, visible from a distance. The testicular volume was determined using a Prader orchidometer.

2.3 | Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Pusan National University Hospital (IRB No. 1712-016-062). Informed consent was waived by the IRB.

2.4 | Statistical analyses

We compared the baseline characteristics of patients. The independent sample *t* test was used for parametric continuous data, the Mann-Whitney *U* test for nonparametric continuous data and the chi-squared test for categorical data. A *p* value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS® for Windows, version 15.0 (SPSS Inc., Chicago, IL).

3 | RESULTS

A total of 954 patients were included, of which 404 had painful varicocele and 550 had painless varicocele. The mean patient age was 26.2 ± 9.8 years. Grade III varicocele was most prevalent, occurring in 637 patients (66.8%), whereas grade II occurred in 253 patients (26.5%) and grade I in 64 patients (6.7%). Left-sided unilateral varicoceles were recorded in 859 patients (90.0%); 9 patients (0.9%) had a right varicocele and the remaining 86 patients (9.1%) had bilateral varicocele. The median time to hospital visit was 12 (interquartile ratio [IQR] 3–24) months (Table 1).

In a comparison of the two groups, the patients with painful varicocele had a lower mean age, lower BMI, higher grade of varicocele, smaller testicular atrophy and shorter time to hospital visit than patients with painless varicocele. In addition, the median serum total testosterone level, total sperm count and sperm concentration and motility were higher in patients with painful varicocele. In multivariate analysis, there were significant differences between the two groups in age, grade III varicocele, testis volume difference, time to hospital visit, total sperm count and sperm concentration (Table 2).

4 | DISCUSSION

Over the past several decades, a number of studies have been conducted on the mechanism by which varicocele induces male infertility (Harrison, Lewis, & Roberts, 1986; Hurt, Howards, & Turner,

TABLE 1 Patients' characteristics

Characteristic	Total (N = 954)	Painful group (N = 404)	Painless group (N = 550)	p-value
Age (years)				
Mean ± SD	26.2 ± 9.8	24.2 ± 9.7	27.7 ± 9.6	0.002 ^{*a}
<18	225 (23.5%)	106 (26.2%)	119 (21.6%)	0.098 ^c
≥18	729 (76.5%)	298 (73.8%)	431 (78.4%)	
BMI (kg/m ²)				
Mean ± SD	22.5 ± 3.2	21.9 ± 2.7	22.9 ± 3.4	0.001 ^{*a}
<18.5	96 (10.0%)	37 (9.2%)	59 (10.7%)	0.041 ^c
18.5–22.9	470 (49.3%)	239 (59.2%)	231 (42.0%)	
23–24.9	196 (20.6%)	76 (18.8%)	120 (21.8%)	
≥25	192 (20.1%)	52 (12.8%)	140 (25.5%)	
Varicocele grade				
I	64 (6.7%)	7 (1.7%)	57 (10.4%)	
II	253 (26.5%)	69 (17.1%)	184 (33.5%)	0.001 ^{*c}
III	637 (66.8%)	328 (81.2%)	309 (56.1%)	
Varicocele laterality				
Left	859 (90.0%)	359 (88.8%)	500 (90.9%)	
Right	9 (0.9%)	7 (1.7%)	2 (0.3%)	0.472 ^c
Bilateral	86 (9.1%)	38 (9.5%)	48 (8.8%)	
Testis volume difference (ml)**				
Median [IQR]	2 [0–3]	0 [0–3]	2 [0–4]	0.001 ^{*b}
<1	267 (30.7%)	208 (56.8%)	59 (11.7%)	0.001 ^{*c}
1–3	331 (38.1%)	101 (27.6%)	230 (45.8%)	
>3	270 (31.2%)	57 (15.6%)	213 (42.5%)	
Time to hospital visit (months)				
Median [IQR]	12 [3–24]	3 [2–7]	24 [18–30]	0.001 ^{*b}
<6	329 (34.5%)	271 (67.0%)	58 (10.5%)	0.002 ^{*c}
6–12	260 (27.2%)	94 (23.2%)	166 (30.1%)	
>12	365 (38.3%)	39 (9.8%)	326 (59.4%)	
Serum total testosterone (ng/dl)				
Median [IQR]	431 [324–541]	471[347–570]	412 [314–520]	0.002 ^{*b}
<350	367 (38.4%)	157 (38.8%)	210 (38.1%)	0.174 ^c
≥350	587 (61.6%)	247 (61.2%)	340 (61.9%)	
Semen analysis, median				
Count, million [IQR]	30.8 [10.0–64.7]	44.1 [17.5–79.1]	26.3 [6.0–58.0]	0.010 ^{*b}
Concentration, million/mL [IQR]	12.4 [4.3–22.9]	14.8 [6.3–26.6]	10.0 [3.3–20.0]	0.014 ^{*b}
Motility, % [IQR]	40 [15–60]	45 [25–65]	30 [6–57]	0.001 ^{*b}

Note. BMI, body mass index; IQR, interquartile range; SD, standard deviation.

^aIndependent sample t test. ^bMann-Whitney U test. ^cChi-squared test. *Statistically significant.

**Unilateral varicocele.

1987; Pryor, Krieg, Evans, Batson, & Turner, 1989). However, the exact mechanism that causes this abnormality remains to be determined. Although most plausible mechanisms have been derived from animal experiments, these theories include an increase in apoptosis, increased sperm DNA damage, oxidative stress, tissue hypoxia, degenerative changes in the seminiferous tubule, immunological

infertility, hormone dysfunction, scrotal hyperthermia and the retrograde flow of adrenal or renal metabolites (Clavijo, Carrasquillo, & Ramasamy, 2017; Zhang et al., 2018).

Clinical and animal model studies have identified a relationship between varicoceles and testicular endocrine and exocrine dysfunction (Pastuszak & Wang, 2015). The main mechanism is via

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value ^a	OR (95% CI)	p-value ^a
Age (years)	0.962 (0.949–0.976)	0.001*	0.897 (0.864–0.970)	0.003*
BMI (kg/m ²)	0.908 (0.872–0.947)	0.042*	0.942 (0.832–1.067)	0.349
Varicocele grade				
I	Reference		Reference	
II	3.054 (1.328–7.019)	0.009*	1.860 (0.413–8.376)	0.419
III	8.644 (3.883–19.240)	0.001*	14.354 (3.247–63.459)	0.002*
Varicocele laterality				
Left	Reference		Reference	
Right	1.879 (0.097–23.603)	0.149	1.562 (0.084–29.015)	0.765
Bilateral	0.427 (0.205–1.723)	0.668	0.547 (0.128–2.331)	0.415
Testis volume difference (ml)**	0.833 (0.779–0.890)	0.001*	0.686 (0.636–0.741)	0.001*
Time to hospital visit (months)	0.235 (0.207–0.264)	0.001*	0.107 (0.049–0.235)	0.001*
Serum total testosterone (ng/dl)	1.002 (1.001–1.003)	0.002*	1.002 (1.000–1.004)	0.104
Semen analysis				
Count, million	1.008 (1.005–1.012)	0.005*	1.007 (1.001–1.015)	0.038*
Concentration, million/ml	1.020 (1.009–1.031)	0.001*	1.020 (1.009–1.031)	0.006*
Motility, %	1.017 (0.998–1.023)	0.402	1.010 (0.996–1.025)	0.167

Note. BMI, body mass index.

^aLogistic regression analysis. *Statistically significant. **Unilateral varicocele.

varicoceles, which induce increased cytoplasmic vacuolisation and atrophy in Leydig cells and decrease the number of Leydig cells (Sirvent et al., 1990). An induced varicocele rat model demonstrated a significant decrease in intratesticular testosterone levels, suggesting a direct effect on Leydig cell function (Zheng et al., 2008). Sertoli cell dysfunction is also observed through decreased androgen-binding protein and transferrin levels in animal models (Li et al., 1999). Serum levels of follicle-stimulating hormone and testosterone are lower in patients with a varicocele and tend to recover following varicocelectomy (Cayan et al., 1999). Inhibin B levels also often improve after a varicocelectomy, suggesting reversible Sertoli cell dysfunction (Fujisawa et al., 2001).

The prevalence of varicocele is generally known to be 4.4% to 22.6%. In particular, the prevalence rate of varicocele among patients with infertility has been reported to be as high as 80% (Will et al., 2011). However, the proportion of patients complaining of pain in varicocele is not well known. Most patients with varicocele are known to be asymptomatic, and pain is reported to be

present in approximately up to 10% (Chung & Lee, 2018; Owen et al., 2017).

To date, the primary indication for varicocelectomy has been focused on men with varicocele with poor semen quality and a normal female partner. The evidence for this indication is that improved testicular function and semen parameters have been identified in many studies after varicocelectomy. After varicocelectomy, the semen parameter was improved in 30% to 60% of patients (Locke, Noparast, & Afshar, 2017), and fertility was recovered in 35% to 46% of patients (Spinelli, Giacomo, Lo Piccolo, Martin, & Messineo, 2010).

Thus, the role and effects of varicocelectomy on male reproductive function are relatively well known and firmly established. However, the results of studies on the therapeutic effect of varicocelectomy on scrotal pain vary among researchers and are inconsistent (Paick & Choi, 2018). After varicocelectomy, the pain resolution rate has been reported to be about 48% to 90%. Although the rate of symptom improvement is high, the complete pain resolution rate is low (Mehta & Goldstein, 2013; Park et al., 2011). Approximately

TABLE 2 Relationships between variables and presence of scrotal pain according to univariate and multivariate analyses

10%–50% of patients are reported to have pain still after surgery (Park et al., 2011). Therefore, patients who do not have satisfactory results from both conservative and surgical treatments are in great frustration and pain, and physicians have a great deal of difficulty in managing these patients.

To overcome these difficulties, researchers have been studying predictive parameters for pain resolution after varicocelectomy. Peterson et al. (Peterson, Lance, & Ruiz, 1998) reported that surgical outcomes were poor in patients with sharp or radiating pain towards the femoral or inguinal area. Yaman, Ozdiler, Anafarta, and Gogus (2000) reported that the failure rate was associated with a high varicocele grade before surgery. In this study, we did not report information about post-operative pain resolution. However, we reported complete resolution in 52.8% of patients who underwent varicocelectomy with scrotal pain, partial resolution in 41.5% and failure in 5.7%. In addition, the success rate was higher when duration of pain before varicocelectomy was less than 6 months (Park et al., 2011).

In the present study, the time to hospital visit by patients with painless varicocele was significantly longer than that of patients with painful varicocele. This can be explained by the fact that the patients with painless varicocele do not have any distinctive symptom of scrotal pain; thus, there is no motivation to visit their physician before they accidentally find a lump in the scrotum or suspect a fertility problem.

Physicians should be concerned about the time to hospital visit because the effect of varicocele on testicular function may be gradual (Gorelick & Goldstein, 1993). Although there is controversy regarding the progressive detrimental effect of varicocele on the testes, it is obvious that varicocele is found more frequently in infertile men, especially in those with secondary infertility (Kantartzi, Goulis, Goulis, & Papadimas, 2007). In line with this, our results show that patients with painful varicocele had better semen parameters than patients with painless varicocele even though they had a higher grade of varicocele. This may be related to the shorter time before visiting the hospital.

The aetiology of scrotal pain associated with varicocele is not completely understood. Proposed mechanisms include compression of nearby neural fibres by the dilated venous complex, increased scrotal temperature, oxidative stress to the testicular parenchyma and tissue ischaemia secondary to venous stasis (Khera & Lipshultz, 2008). In our study, the grade of varicocele in patients with pain was significantly higher than in the painless group, which seems to support this hypothesis.

We thought that the lower mean age of patients with painful varicocele was related to earlier visits to the hospital by recognition of varicocele due to scrotal pain. In addition, the reason for the larger testis volume difference and lower sperm count and concentration in patients with painless varicocele seems to be related to the longer period of time between abnormality recognition and hospital visit. These findings suggest that although scrotal pain induced by varicocele is difficult to treat, it may lead to an earlier diagnosis and treatment and provide an opportunity to avoid impairment of future fertility. However, further studies

are needed to determine whether the final pregnancy rate among patients with pain is higher after treatment than among patients without pain.

There are several important limitations to this study. First, this is a single-centre, retrospective study. The lack of an even distribution of patients with regard to ethnicity, comorbidities and location of varicocele may have resulted in bias. Second, we did not analyse the quality or severity of the pain. Although we measured the severity of pain using an analog visual pain scale at the interview of the patient and recorded the quality of the pain, we could not obtain enough data for the final analysis. Third, due to the lack of data in the sperm functional assay (i.e., hyposmotic swelling test, eosin-nigrosin stain) and pregnancy rates among the patients with painful varicocele, we could not compare those parameters between the two groups. Finally, this study lacked further analysis of the reasons for late visits to the hospital even after painless patients became aware of the varicocele.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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