international journal of andrology, 21:256–260 (1998)

Improvement of sperm count and motility after ligation of varicoceles detected with colour Doppler ultrasonography

F. H. PIERIK,*†‡ J. T. M. VREEBURG,*† TH. STIJNEN,** J. H. VAN ROIJEN,*†§ G. R. DOHLE,*§ J. S. LAMÉRIS,¶ T. TIMMERS‡ and R. F. A. WEBER*†

Departments of *Andrology, §Urology and ¶Radiology, University Hospital Dijkzigt Rotterdam, and Departments of †Endocrinology and Reproduction, ‡Medical Informatics and **Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Erasmus University Rotterdam, The Netherlands

Summary

The debate regarding the efficacy of varicocele ligation for improvement of semen parameters and pregnancy rates is ongoing. In addition, no consensus exists as to the benefit of treatment of subclinical varicoceles. The aim of this study was to investigate, retrospectively, the effect of high ligation of both subclinical and clinical varicoceles on sperm count and motility. The value of several factors from history-taking and physical examination for the prediction of successful varicocelectomy was analysed. A total of 139 patients, operated on for a unilateral varicocele on the left side, were studied. Varicoceles were subclinical in 73 patients, based on colour Doppler ultrasonography, and 66 varicoceles were clinical, based on palpation in addition to ultrasonography. Comparison of semen parameters before and after surgery revealed a significant improvement. The median sperm count increased from 10.0 to 14.7, and from 18.2 to 28.6 million/ejaculate, in patients with subclinical and clinical varicoceles, respectively ($p < 0.001$). The percentage improvement in median sperm count in subclinical varicoceles was not statistically different from the improvement in clinical varicoceles. Mean progressive motility improved significantly after ligation ($p < 0.001$). The improvement in motility in subclinical varicoceles, from 16 to 23%, was significantly larger than the 24 to 27% improvement in clinical varicoceles. The increase in sperm count was related positively to testicular volume before surgery ($p < 0.05$). The increase in sperm motility was significantly lower in patients with a history of cryptorchidism ($n = 22$, $p < 0.05$). The present data show that ligation of varicoceles detected using Doppler ultrasonography, whether palpable or not, results in an increase in sperm concentration and motility.

Keywords: colour Doppler ultrasonography, semen parameters, subclinical varicocele, varicocele ligation

Correspondence: Frank H. Pierik, Department of Andrology, University Hospital Dijkzigt Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

Introduction

Varicocele is the most frequently identified male factor in couples consulting with fertility problems. Varicocele has been associated with adverse effects on sperm concentration, motility and morphology, testis size and histology, blood hormone levels and pregnancy rates (Kass & Reitelman, 1995). Most studies on the effect of varicocelectomy have reported improvement in male fertility, but the degree of improvement varies substantially. Mordel *et al.* (1990) reviewed 50 reports, in which improvement of semen parameters and pregnancy rates after spermatic vein ligation varied from 0 to 92% (mean 57%), and 0 to 63% (mean 36%), respectively. The results of two more recent prospective, randomized controlled studies also reported different outcomes of varicocele occlusion in terms of alteration in sperm quality and pregnancy rate (Madgar *et al.*, 1995; Nieschlag *et al.*, 1995). Possible reasons for the differences in outcome of varicocelectomy between studies are differences in the composition of patient groups (e.g. duration of infertility, age, the size of the varicocele and preoperative semen characteristics; Hargreave, 1995).

The size of the varicocele may influence the outcome of varicocele ligation. Marsman & Schats (1994) reviewed the literature on the controversial concept that the subclinical varicocele (SV) is detrimental to spermatogenesis, and that SV ligation improves semen quality. Like the more generally accepted treatment of the clinical varicocele (CV), the reported effects of SV ligation on sperm characteristics and pregnancy rates show a substantial variation, and it is unclear whether SV and CV patients benefit similarly from varicocele treatment.

Moreover, no consensus exists as to the method of choice for diagnosing varicoceles. Palpation can be performed routinely, but a low specificity and sensitivity have been reported (Trum *et al.*, 1996). Since palpation is not accurate, other modalities are utilized to identify CV and SV (e.g. thermography, venography, colour Doppler ultrasonography, Doppler stethoscope).

In the current paper, we present the effect of the Palomo procedure on sperm concentration and motility in 139 patients with a varicocele, detected using colour Doppler ultrasonography, that was either palpable or not. The cohort of SV ($n = 73$) is one of the largest reported so far. Factors that may predict successful varicocelectomy were analysed.

Patients and methods

Patients

A group of 139 patients who underwent retroperitoneal high varicocele ligation (Palomo, 1949) were included in this study. Varicoceles were graded as clinical if the distension of the pampiniform plexus was visible or palpable (with or without Valsalva manoeuvre), with the patient in the upright posture, and were confirmed by colour Doppler ultrasonography (CDU). Varicoceles were graded subclinical whenever palpation was negative, but CDU was positive. Since varicocele is defined as venous reflux in the pampiniform plexus, usually caused by incompetent valves and resulting in dilatation of the veins, the varicocele can be diagnosed both on the basis of reflux and venous diameter. We used CDU (high-frequency duplex echotransducer ≥ 5 MHz) to determine venous diameter (ultrasound) and direction and velocity of bloodflow (Doppler sonography). Ultrasonography was considered positive when the diameter of veins was 3 mm or more with increasing diameter during the Valsalva manoeuvre or when changing from supine to erect posture (McClure & Hricak, 1986). Doppler ultrasound was considered positive when increased venous retrograde flow in the pampiniform plexus was detected in erect posture, or during the Valsalva manoeuvre (Petros *et al.*, 1991). Varicocele ligation was performed using the Palomo approach (Palomo, 1949). Inclusion criteria for surgery were infertility (with a duration of more than 1 year), presence of a varicocele and subnormal sperm parameters (< 50% progressive motility, < 20 million spermatozoa/mL, or <40 million spermatozoa/ejaculate). Azoospermic patients with varicocele were not treated. The age, duration of infertility, testicular volume prior to surgery (Prader orchidometer), type of infertility (primary or secondary) and history of cryptorchidism and accessory gland infection (World Health Organization, 1992c) for the study population are given in Table 1.

Semen analyses were performed according to WHO guidelines, and comprised volume, sperm concentration and percentage progressive motility (World Health Organization, 1992b). The total sperm count (sperm concentration × ejaculate volume) was used as the outcome variable instead of sperm concentration, to correct for differences in ejaculate volumes between and within patients. Sperm antibodies were detected with the direct mixed antiglobulin (MAR)

Table 1. General characteristics of the study population. Values are means ± SD or percentages

	Subclinical varicoceles ($n = 73$)	Clinical varicoceles ($n = 66$)
Age at surgery (years)	32.7 (4.6)	32.6 (4.8)
Years of infertility	3.8 (2.5)	2.9* (1.6)
Total testicular volume (mL)	28.4 (7.2)	30.0 (8.6)
Primary infertility (%)	89	86
Cryptorchidism (%)	23	8*
Accessory gland infection (%)	5	5
Sperm antibodies (%)	5	6

*$p < 0.05$, clinical versus subclinical varicocele.

reaction test (SpermMar IgG Test, Ferti Pro, N.U., Beernen, Belgium). MAR binding of 40% or more of motile spermatozoa was regarded as positive. Semen samples were obtained after a 2–5day abstinence period. All semen analyses in the 2 years before varicocele ligation and in the period from 70 days to 2 years after ligation were assessed. The mean number of assessed semen analyses was 2.3 (range 1–7) before and 2.4 (range 1–8) after ligation.

Data management and analysis

Practically all patient data of the Andrology outpatient clinic are stored electronically in subsystems of the hospital information system. To exploit the potential of these separate data collections fully, an Andrology Research Information System (ARIS) has been developed, based on the ORCA (Open Record for Care) electronic patient record, that validates and integrates these data sources, facilitating clinical research on patient data (Pierik *et al*., 1997).

For patients who fulfilled inclusion criteria, data were retrieved from ARIS by a query on: date of birth, primary/secondary infertility, duration of infertility, history of cryptorchidism, history of accessory gland infection, semen analyses, date of the varicocele ligation, testicular volume and the result of scrotal CDU.

The effect of surgery on total sperm count was assessed using a linear regression model with random coefficients (SAS program Proc Mixed). In the model, the effect of surgery was represented by a surgery indicator variable being zero for semen analyses before the operation, and being one for semen analyses after the operation. To account for dependence introduced by the fact that each patient had two or more measurements, model intercept and the regression coefficient of surgery were assumed to be random and possibly correlated (the correlation representing the association between pre-surgery sperm count or motility level and the surgery effect). To obtain a normally distributed dependent variable, sperm count was logarithmically transformed. Since absolute increases in means on the logarithmic scale correspond to relative increases in the median on the original scale, the results for sperm count are expressed using medians. To investigate whether a factor (e.g. CV vs. SV) modified the surgery effect, the factor and its interaction with the surgery indicator variable were added to the model.

The effect of surgery on motility was assessed analogously. Because no normalizing transformation could be found, sperm motility was used untransformed in the regression analysis. To account for the non-normal distribution of motility, the standard errors of the regression coefficients were estimated robustly, i.e. without using the normality and homoscedasticity assumption (SAS Institute Inc., 1996).

Differences in means between groups were tested with the independent-samples *t*-test, and differences in percentages with the χ^2 method. Means are presented with standard errors. Two-sided *p*-values < 0.05 were considered significant, and statistical analyses were carried out using the SAS System® statistical software package.

Results

Effect of varicocelectomy on total sperm count

Treatment of the varicocele resulted in a statistically significant increase in the median total sperm count ($p < 0.001$, Table 2). The positive relative effect of surgery on the number of spermatozoa in the ejaculate was not significantly different for CV and SV. The median sperm count and mean progressive motility were higher in CV than in SV ($p < 0.05$). There was a statistically significant interaction between total testicular volume and the effect of surgery on the total sperm count, irrespective of the varicocele size ($p < 0.001$); this amounted to a 2.5% higher sperm count for each extra 1 mL total testicular volume. Subjects with a history of cryptorchidism had a lower initial sperm count (4.6 million/ejaculate) which was $\approx$ 30% of that found in other patients (17.2 million/ejaculate; $p < 0.001$), but the relative increase in total sperm count was not statistically different compared with other varicocele patients. Duration of infertility, age at surgery, primary/secondary infertility, accessory gland infection and antibody-coated spermatozoa had no association with improvement in sperm count. In 28% of the cases, no improvement in total

Table 2. Mean semen parameters (95% confidence interval) before and after varicocele ligation in all patients and in clinical/subclinical varicocele subgroups

	N	Median total sperm count (10^6/ejacul.)[a]		Mean progressive motility (%)[a]	
		before	after	before	after
All	139	13.9 (11.0–17.7)	21.2 (16.6–27.0)	21 (18-23)	25 (22–28)
Subclinical	73	10.0 (7.8–14.2)	14.7 (10.2–21.0)	16 (13-19)	23 (19–27)
Clinical[c]	66	18.2 (12.8–24.8)	28.6 (20.7–39.4)	24 (20-28)	27[b] (22–30)

[a] $p < 0.001$, before versus after varicocele ligation in all patients [b] $p < 0.05$, greater motility improvement in subclinical versus clinical varicocele [c] $p < 0.05$, higher basal total sperm count and progressive motility in clinical varicocele versus subclinical varicocele.

sperm count was observed. The sperm count before varicocele surgery was not correlated with the improvement of sperm count postsurgery ($r = -0.21$, $p = 0.11$).

Effect of varicocelectomy on progressive sperm motility

Varicocele treatment significantly increased progressive sperm motility ($p < 0.001$, Table 2). In SV, the improvement in sperm motility was larger than in CV ($p < 0.05$). Basal sperm motility was lower in SV vs. CV ($p < 0.05$). Duration of infertility, age at surgery, primary/secondary infertility, accessory gland infection, bilateral testicular volume and antibody-coated spermatozoa were not correlated with the improvement in sperm motility. Patients with a history of cryptorchidism had a significantly lower progressive sperm motility prior to surgery (7%) when compared with other varicoceles (23%), and the effect of surgery on motility was negligible. In 31% of cases, no improvement in progressive sperm motility was observed. The percentage of progressive motility before surgery was not correlated with the magnitude of the improvement of motility following varicocelectomy ($r = -0.20$, $p > 0.1$).

Discussion

Our finding that varicocelectomy improves sperm counts and motility is in agreement with the majority of reports. Mordel *et al.* (1990) reviewed 38 varicocele studies that reported the percentage of patients with improvement in sperm parameters (range 0–92%). Overall, an improvement in semen parameters was seen in 57% of the total of 4654 patients in these studies, calculated as a weighted mean. In only three of these studies was no increase in sperm characteristics reported. However, most of the reviewed studies did not include untreated control groups. In two more recent, randomized controlled studies, no alteration in sperm parameters was observed in the control groups during 1 year of follow-up, whereas the total sperm count improved significantly in treated patients (Nieschlag *et al.*, 1995; Madgar *et al.*, 1995). Improvement in sperm motility is not a consistent result of varicocele surgery, and was only statistically significant in one of these two studies (Madgar *et al.*, 1995).

There is a large variation in the magnitude of the effect of varicocelectomy on semen parameters between studies (reviewed by Schlesinger *et al.*, 1994). This variation has been attributed to differences in size of the varicocele, baseline semen quality, duration of infertility, testicular volume and the reliability of diagnostic and therapeutic methods, among other possibilities (Kass & Reitelman, 1995).

We found a positive correlation between initial testicular volume and the improvement in sperm count, whereas a history of cryptorchidism gave a significantly smaller increase in sperm motility. From the regression equation, a nullifying effect of small testis size on improvement in sperm count was calculated at a total bilateral volume of smaller than 12 mL, which was present in only one patient in our study population (with testes of 5 mL on both sides). A smaller testicular volume may indicate more progressive or additional testicular pathology, which does not respond to surgery. This may also explain the lack of improvement in sperm motility following varicocele treatment in the subpopulation with a history of cryptorchidism. The age of the man, duration of infertility and sperm count and motility before surgery were not significant indicators of the benefit of varicocelectomy in our population.

A reason that has been postulated for differences in treatment outcome is variance in the size of the varicocele between study populations. Both in SV and CV, testicular atrophy has been observed (Zini *et al.*, 1997). Several authors reported equal semen improvements in SV vs. CV following surgery, or reported a slightly higher improvement in SV (Van der Vis-Melsen *et al.*, 1982; Marsman, 1985; McClure *et al.*, 1991; Petros *et al.*, 1991; Marsman *et al.*, 1995). A greater increase in semen quality in CV compared with SV was noted by Tinga *et al.* (1984), Bsat & Masabni (1988) and Jarow *et al.* (1996). Our results are in line with the argument that ligation of both SV and CV is effective in terms of improvement in spermatogenesis. We found significant improvement of the sperm count, irrespective of the grade of the varicocele, and a significantly larger increase in progressive sperm motility in SV.

A comparison of SV and CV is difficult as the CV diagnosis is based on palpation, which is less objective and more prone to errors than is ultrasonography, for example. The accuracy of detection of varicoceles by physical examination has been shown to be correlated with the experience and expertise of the physician (World Health Organization, 1992a). The reported false positive rate of palpation compared with venography varies from 24 to 67% (World Health Organization, 1985; Pochaczevsky *et al.*, 1986; Petros *et al.*, 1991; Trum *et al.*, 1996), and was only 5% in one study (Comhaire *et al.*, 1976). Since palpation is not a very accurate screening method, we suggest routine performance of CDU, which may find additional pathology (e.g. spermatocele, testicular tumours; Nashan *et al.*, 1990) and can measure testicular volume accurately (Behre *et al.*, 1989). Instead of grading the varicocele as SV or CV (I-III), grading could be based on vein diameters or reflux measured with CDU. The diagnosis of varicocele on the basis of CDU had been compared with venography by others. A good sensitivity and specificity of 90–98% for CDU was found (Gonda *et al.*, 1987; Petros *et al.*, 1991; Trum *et al.*, 1996). Venography, however, may also produce false results (Mali *et al.*, 1986; Yarborough *et al.*, 1989).

In conclusion, we studied a large group of SV detected by routine colour Doppler ultrasonography, and a group of CV. Both were treated effectively in terms of semen improvement. We reason that as long as treatment of CV is accepted as an effective treatment of subfertility, the treatment of SV in infertile men with subnormal semen parameters is equally legitimate. Colour Doppler ultrasonography seems to be a good method for screening for varicoceles in infertile men, that can be treated effectively.

References

Behre, H. M., Nashan, D. & Nieschlag, E. (1989) Objective measurement of testicular volume by ultrasonography: evaluation of the technique and comparison with orchidometer estimates. *International Journal of Andrology*, **12**, 395–403.

Bsat, F. A. & Masabni, R. (1988) Effectiveness of varicocelectomy in varicoceles diagnosed by physical examination versus Doppler studies. *Fertility and Sterility*, **50**, 321–323.

Comhaire, F., Monteyne, R. & Kunnen, M. (1976) The value of scrotal thermography as compared with selective retrograde venography of the internal spermatic vein for the diagnosis of 'subclinical' varicocele. *Fertility and Sterility*, **27**, 694–698.

Gonda, R. L. Jr, Karo, J. J., Forte, R. A. & O'Donnell, K. T. (1987) Diagnosis of subclinical varicocele in infertility. *American Journal of Roentgenology*, **148**, 71–75.

Hargreave, T. B. (1995) Debate on the pros and cons of varicocele treatment – in favour of varicocele treatment. *Human Reproduction*, **10**, 151–157.

Jarow, J. P., Ogle, S. R. & Eskew, L. A. (1996) Seminal improvement following repair of ultrasound detected subclinical varicoceles. *Journal of Urology*, **155**, 1287–1290.

Kass, E. J. & Reitelman, C. (1995) Adolescent varicocele. *Urologic Clinics of North America*, **22**, 151–159.

Madgar, I., Weissenberg, R., Lunenfeld, B., Karasik, A. & Goldwasser, B. (1995) Controlled trial of high spermatic vein ligation for varicocele in infertile men. *Fertility and Sterility*, **63**, 120–124.

Mali, W. P., Oei, H. Y., Arndt, J. W., Kremer, J., Coolsaet, B. L. & Schuur, K. (1986) Hemodynamics of the varicocele. Part I. Correlation among the clinical, phlebographic and scintigraphic findings. *Journal of Urology*, **135**, 483–488.

Marsman, J. W. (1985) Clinical versus subclinical varicocele: venographic findings and improvement of fertility after embolization. *Radiology*, **155**, 635–638.

Marsman, J., Brand, R., Schats, R. & Bernardus, R. E. (1995) Clinical and subclinical varicocele: a useful distinction? *European Journal of Obstetrics and Gynecology and Reproductive Biology*, **60**, 165–169.

Marsman, J. W. & Schats, R. (1994) The subclinical varicocele debate. *Human Reproduction*, **9**, 1–8.

McClure, R. D. & Hricak, H. (1986) Scrotal ultrasound in the infertile man: detection of subclinical unilateral and bilateral varicoceles. *Journal of Urology*, **135**, 711–715.

McClure, R. D., Khoo, D., Jarvi, K. & Hricak, H. (1991) Subclinical varicocele: the effectiveness of varicocelectomy. *Journal of Urology*, **145**, 789–791.

Mordel, N., Mor-Yosef, S., Margalioth, E. J., Simon, A., Menashe, M., Berger, M. & Schenker, J. G. (1990) Spermatic vein ligation as treatment for male infertility. Justification by postoperative semen improvement and pregnancy rates. *Journal of Reproductive Medicine*, **35**, 123–127.

Nashan, D., Behre, H. M., Grunert, J. H. & Nieschlag, E. (1990) Diagnostic value of scrotal sonography in infertile men: report on 658 cases. *Andrologia*, **22**, 387–395.

Nieschlag, E., Hertle, L., Fischedick, A. & Behre, H. M. (1995) Treatment of varicocele: counselling as effective as occlusion of the vena spermatica. *Human Reproduction*, **10**, 347–353.

Palomo, A. (1949) Radical cure of varicocele by a new technique: preliminary report. *Journal of Urology*, **61**, 604–607.

Petros, J. A., Andriole, G. L., Middleton, W. D. & Picus, D. A. (1991) Correlation of testicular color Doppler ultrasonography, physical examination and venography in the detection of left varicoceles in men with infertility. *Journal of Urology*, **145**, 785–788.

Pierik, F. H., Van Ginneken, A. M., Timmers, T., Stam, H. & Weber, R. F. A. (1997) Restructuring of routinely collected patient data: ORCA applied to andrology. *Methods of Information in Medicine*, **36**, 184–190.

Pochaczevsky, R., Lee, W. J. & Mallett, E. (1986) Management of male infertility: roles of contact thermography, spermatic venography, and embolization. *American Journal of Roentgenology*, **147**, 97–102.

SAS Institute Inc. (1996) The mixed procedure. In: *SAS/STAT®*-Software: changes and enhancements through release 6.11, Chapter 18. SAS Institute, Cary, North Carolina.

Schlesinger, M. H., Wilets, I. F. & Nagler, H. M. (1994) Treatment outcome after varicocelectomy. A critical analysis. *Urologic Clinics of North America*, **21**, 517–529.

Tinga, D. J., Jager, S., Bruijnen, C. L., Kremer, J. & Mensink, H. J. (1984) Factors related to semen improvement and fertility after varicocele operation. *Fertility and Sterility*, **41**, 404–410.

Trum, J. W., Gubler, F. M., Laan, R. & Vanderveen, F. (1996) The value of palpation, varicoscreen contact thermography and colour doppler ultrasound in the diagnosis of varicocele. *Human Reproduction*, **11**, 1232–1235.

Van der Vis-Melsen, M. J., Baert, R. J., van der Beek, F. J. & de Wringer, P. J. (1982) Sensitivity of scrotal scintigraphy in the diagnosis of varicocele. *Clinical Nuclear Medicine*, **7**, 287–291.

World Health Organization (1985) Comparison among different methods for the diagnosis of varicocele. *Fertility and Sterility*, **43**, 575–582.

World Health Organization (1992a) The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. *Fertility and Sterility*, **57**, 1289–1293.

World Health Organization (1992b) *WHO Laboratory Manual for the Examination of Human Semen and Semen–Cervical Mucus Interaction*, 3rd edn. Cambridge University Press, Cambridge.

World Health Organization (1992c) *WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple* (ed. P. J. Rowe, F. H. Comhaire, T. B. Hargreave & H. J. Mellows). Cambridge University Press, Cambridge.

Yarborough, M. A., Burns, J. R. & Keller, F. S. (1989) Incidence and clinical significance of subclinical scrotal varicoceles. *Journal of Urology*, **141**, 1372–1374.

Zini, A., Buckspan, M., Berardinucci, D. & Jarvi, K. (1997) The influence of clinical and subclinical varicocele on testicular volume. *Fertility and Sterility*, **68**, 671–674.

Received 24 March 1997; accepted 15 April 1998