Sclerotherapy of Idiopathic Hydroceles and Epididymal Cysts: A Historical Comparison Trial of 5% Phenol versus Tetracycline

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ABSTRACT

Operating time for idiopathic hydroceles and epididymal cysts is scarce as these conditions compete with an increasing caseload of more consequential surgical disease. Therapy is often relegated to repeated aspiration. Sclerotherapy appears to be effective in a majority of published trials, but comparative effectiveness, efficacy and safety of most agents, including phenol versus *tetracycline, has not been established. A deliberate strategy of re-treatment until cure is not universally practised, with surgery still being offered after single-treatment failures. Two trials, the first consisting of 53 scrotal cysts treated with 5% phenol-in-water and the second, 42 cysts treated with tetracycline, are compared for effectiveness, efficacy and safety of sclerotherapy* per se *and of re-treatment. Intention-to-treat analysis yields similar cure rates (no re-accumulation three months after last injection) for phenol and tetracycline (83% and 81% respectively,* p *= 0.8). Per-protocol analysis also yields similar cure rates (100% and 97% respectively,* p *= 0.26) and mean number of injections to cure (1.34 and 1.12 respectively,* p *= 0.069), with range 1–4 and 1–3 respectively. Severe pain following tetracycline injection required administration of pre-injection cord block. Other complications occurred equally (25% and 25.7% respectively,* p *= 0.94) and were trivial except for one case of chronic haematocele treated by orchiectomy in the tetracycline group. Phenol (5%) and tetracycline are equally efficacious sclerosants for idiopathic scrotal cysts, achieving almost 100% cure with re-treatment and matching the efficacy of surgery. Concern about post-treatment fertility applies equally to surgery and demands informed consent for both modalities.*

Escleroterapia de los Hidroceles Idiopáticos y los Quistes Epididimales: un Ensayo Comparativo Histórico del Fenol al 5% frente a la tetraciclina

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RESUMEN

El tiempo de operación para los hidroceles y los quistes epididimales es escaso, ya que estas condiciones triviales compiten con una creciente carga de casos de enfermedades quirúrgicas de mayores consecuencias. La terapia es a menudo relegada a una aspiración repetida. La escleroterapia parece ser efectiva en la mayoría de los ensayos publicados, pero no se han establecido la seguridad, eficacia y efectividad comparativa de la mayor parte de los agentes, incluyendo el fenol, frente a la tetraciclina. No se practica universalmente una estrategia deliberada de re-tratamiento hasta la cura, ofreciéndose todavía la cirugía, luego de fracasos con tratamientos individuales. Dos ensayos, el primero consistente en 53 quistes escrotales tratados con fenol acuoso al 5%, y el segundo, en 42 quistes tratados con tetraciclina, se comparan en cuanto a efectividad, eficacia y seguridad para la escleroterapia per se y para el re-tratamiento. El análisis de intención de tratamiento produce tasas de curación similares (no hay re-acumulación 3 meses después de la última inyección) para el fenol y la tetraciclina (83% y 81% respectivamente, p *= 0.8). El análisis por protocolo también produce tasas de curación similares (100% y 97% respectivamente,* p *= 0.26) y el número medio de inyecciones para curar (1.34 y 1.12 respectivamente,* p *= 0.069), con rangos de 1–4 y 1–3 respectivamente. El dolor*

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severo tras la inyección de tetraciclina requirió hacer un bloqueo espinal de pre-inyec-ción. Asimismo ocurrieron otras complicaciones (25% y 25.7% respectivamente, p = *0.94) y fueron triviales, con excepción de un caso de hematoceles crónicos tratado mediante orquiectomía en el grupo de tetraciclina. El fenol (5%) y la tetraciclina poseen igual eficacia como esclerosantes de los quistes escrotales idiopáticos, ya que logran una curación de casi 100% con el re-tratamiento, e igualan la eficacia de la cirugía. El problema de la fertilidad posterior al tratamiento, se presenta también en el caso de la cirugía y requiere del consentimiento informado para ambas modalidades.*

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INTRODUCTION

Operating time for surgical treatment of idiopathic hydroceles and epididymal cysts has become scarce as these conditions must compete with the increasing caseload of more consequential surgical disease for space, time and personnel. Often, patients are relegated to a regime of repeated aspirations as they await an opening for surgery. Sclerotherapy with either 2.5% phenol, 3% phenol or tetracycline appears to be variably effective after a single injection (1–10), with concentrations of tetracycline from 2.5% to 10% appearing to have equal efficacy (11), but some studies have found tetracycline to be ineffective (12–14) (Table 1.).

Table 1: Cure rates for idiopathic scrotal cysts after one injection of sclerosant.

Study	Sclerosant		
	Tetracycline*	2.5% Phenol	3% Phenol
Ozdemir (8)			58%
Savion et al (9)		51.6%	
Shan et al (10)		47.5%	
Bullock and Thurston (1)	87%		
Daehlin *et al* (2)	83%		
Honnens *et al* (3)	77%		
Levine and DeWolf (4)	75%		
Lopez Laur and Parisi (5)	69.5%		
Losada Guerra and Hernandez (6)	79%		
Miskowiak and Christensen (7)	85%		
Badenoch et al (12),Ozkan *et al* (14)	33.3%		
Breda *et al* (13)	20%		

* Concentrations of tetracycline solution from 2.5% to 10% appear to have equal efficacy (11).

Although a deliberate strategy of re-treatment until cure has been practised with both phenol and tetracycline (1, 4, 8–10, 15–17), others recommend surgery after single-treatment failure (3, 6). There are no studies comparing efficacy and safety of phenol and tetracycline.

In the first of the two trials compared in this study, 5% phenol-in-water was used in the hope of achieving higher cure rates after one injection than those reported for 2.5% and 3% phenol in Table 1. In the second trial, tetracycline-for-injection was used because it was then more readily available than phenol. Tetracycline-for-injection is no longer available but doxycycline and minocycline injections appear to have similar efficacy (18) and solutions of tetracycline may be prepared from oral capsules by dissolving in saline and passing through a sterile membrane (19).

Phenol and tetracycline are assessed separately for effectiveness, efficacy and safety of sclerotherapy *per se* and of re-treatment of failures, and the results compared. Sclerotherapy as an alternative treatment to surgery is discussed, including the comparative threat to fertility.

SUBJECTS AND METHODS

Criteria for selection of cases were the same in both trials. A case was either an idiopathic vaginal hydrocele (clear, straw coloured fluid) or epididymal cyst (cloudy white fluid). Exclusions were scrotal cysts present for less than three months or in which there were antecedents suggestive of inflammation (urinary tract infection, pain, tenderness), testicular torsion, trauma or tumour (*ie* cysts which might have been secondary rather than idiopathic). Only one of bilateral cysts were to be selected for sclerotherapy in men under 60 years but this exclusion criterion became irrelevant since bilateral cysts were only found in men over 60 years.

Informed consent was obtained in each case. The scrotum was cleaned and draped and the cyst made tense by grasping between the fingers and thumb of the left hand. A 16 gauge intravenous cannula was then inserted smartly through the anaesthetized skin over the proximal half of the cyst and into the sac. The cannula was advanced another 5mm or so after the first appearance of fluid in the reservoir (to ensure placement well within the sac, but not so far that the needle may puncture the testis). The needle was then withdrawn about 5 mm but remained within the cannula (to prevent kinking) and the cannula advanced to the hilt. If the cannula is not advanced to the hilt or the puncture is made over the distal half of the sac, there is a risk of the sac slipping off the cannula as cyst decompression occurs with the tip of the cannula being dislodged into the subcutaneous tissue.

The fluid was then removed completely by a combination of aspiration and drainage. As the volume of fluid decreases, aspiration tends to suck the wall of the sac into the cannula and block it. When this starts to happen, the remaining fluid should be passively drained, encouraged by gentle manipulation of the scrotum. The testis and cord are then carefully palpated for tenderness and tumour, care being taken not to dislodge the cannula. Fluid is not sent for culture nor cytology. When cord block is necessary, it should be

performed at this stage. Sclerosant is instilled not less than 5 minutes after cord block.

In the first trial, the sclerosant solution was 5% phenol-in-water. The volume instilled depended on the volume of aspirate, with 15 cc instilled for up to 100 cc of aspirate, 20 cc for 101 cc to 300 cc, 25 cc for 301 to 500 cc and 30 cc for more than 500 cc of aspirate. No local anaesthetic was added to the solution and no cord block was performed.

In the second trial, 500mg of tetracycline injection in 5 cc of solution was instilled regardless of the volume of aspirate. After three (five cysts) of the first seven patients receiving tetracycline instillation suffered excruciating pain, cord block with 20 cc of 0.5% lidocaine was introduced for all subsequent cases.

Patients were advised to wear tight fitting underwear for a few weeks. Each was reviewed at intervals of six weeks unless there was an acute complication requiring urgent attention. At each review, complaints were noted, the scrotum examined and aspiration performed if necessary. Sclerotherapy was repeated if the aspirate exceeded 50 cc but was not performed if the aspirate was less, was blood stained or there was marked thickening of the scrotal contents. Cysts with no re-accumulation of fluid three months after the last treatment were considered cured.

Data for both studies were entered into a single database in STATA Version 8 for analysis. Classical bivariate statistical analyses were performed.

RESULTS

Table 2 summarizes characteristics of the cysts treated in both studies, as well as the results of intention-to-treat and perprotocol analyses and comparisons. Tables 3 and 4 display statistical comparisons between the cure rates after single injections of 5% phenol and tetracycline respectively and the studies tabulated in Table 1.

Nine cysts treated with phenol were accompanied by mild, acute pain. Three of the first nine cysts treated with tetracycline were accompanied by excruciating acute pain minutes after instillation and one by mild pain. After that, all treatments in the tetracycline group were preceded by spermatic cord block, resulting in a marked, statistically significant decrease in the occurrence of severe acute pain to 3% (1/33) (p = 0.026, Fisher's exact test). Mild pain occurred in 6.1% (2/33) after cord block.

Other complications included acute haematocele (all 5 cases of which occurred in the phenol group) and thickening or swelling of scrotal contents. Acute haematoceles were aspirated at weekly intervals and none was surgically drained. All five cases settled completely and only one required a second injection for cure. All cases of thickening or swelling of scrotal contents eventually subsided completely, except for one case of hydrocele in the tetracycline group in which a persistent, markedly swollen testis occurred after the third injection and which was treated by orchiectomy.

Table 2: Characteristics and results of intention-to-treat and per-protocol analyses of scrotal cysts treated with 5% phenol and tetracycline.

	5% Phenol	Tetracycline	p-value
Number of cysts treated	53	42	
Number of patients	41	35	
Age in years – median (range)	64 (38–88)	64 (39–87)	
Volume of aspirate – mean (range) (Per-protocol)	216 (80–750)	251 (50–760)	0.27 (t-test)
Cysts censored (Lost to follow-up or withdrawn)	9 (17%)	7 (16.7%)	0.97(z-test)
Cysts cured* (Intention-to-treat)	44/53 (83%)	34/42 (81%)	0.8 (z-test)
Cysts cured after 1 injection (Per-protocol)	31/44 (70.5%)	31/35 (88.6%	0.052 (z-test)
Cysts cured after 2 injections (Per-protocol)	43/44 (97.7%)	33/35 (94.3%)	0.43 (z-test)
Cysts cured after 3 injections (Per-protocol)	43/44 (97.7%)	34/35 (97%)	0.85 (z-test)
Cysts cured after 3 to 4 injections (Per-protocol)**	44/44 (100%)	34/35 (97%)	0.26 (z-test)
Mean number of injections to cure (and range)	1.34 (1–4)	1.12 (1–3)	0.069 (t-test)
Complication risk (excluding pain)*** (Per-protocol)	11/44 (25%)	9/35 (25.7%)	0.94 (X^2 test)

*Cure defined as no re-accumulation 3 months after last injection.
**Phenol group reached maximum cure rate after 4 injections and tetracycline group after 3. The only case not cured (tetracycline group) received 3 injections.
***Complications included haematocele and thickening or swelling of scrotal contents.

Table 3: Comparisons between cure rate of 70.5% for idiopathic scrotal cysts after one injection of 5% phenol from this study and cure rates for 3% and 2.5% phenol from studies reported in Table 1.

Study	Cure rate	p-value (one sample test)
Ozdemir (8) (3% phenol)	58%	0.094
Savion *et al* (9) (2.5% phenol)	51.6%	0.012
Shan *et al* (10) (2.5% phenol)	47.5%	0.002

Table 4: Comparisons between cure rate of 88.6% for idiopathic scrotal cysts after one injection of tetracycline from this study and cure rates from studies reported in Table 1.

Study	Cure rate	p-value (one sample test)
Bullock and Thurston (1)	87%	0.78
Daehlin *et al* (2)	83%	0.38
Honnens *et al* (3)	77%	0.1
Levine and DeWolf (4)	75%	0.064
Lopez Laur and Parisi (5)	69.5%	0.014
Losada Guerra and Hernandez (6)	79%	0.16
Miskowiak and Christensen (7)	85%	0.55
Badenoch et al (12),Ozkan *et al* (14)	33.3%	< 0.001
Breda *et al* (13)	20%	< 0.001

Histology showed chronic haematocele. There were no infections and no extravasation of sclerosant. One patient in the phenol group developed a tumour within the spermatic cord at the level of the external inguinal ring. Histological examination revealed a "fibrous pseudotumour".

In the tetracycline group, the case of persistent testicular swelling treated by orchiectomy occurred after a third injection but in no other case did any new complication (or exacerbation of a previously observed complication) occur after the first injection. It therefore appears that for tetracycline, subsequent injections are associated with a lower complication rate than first injections. These data are not available for the phenol group.

The occurrence of a complication was not associated with a higher cure rate after one injection in either the phenol group ($p = 0.26$, Fisher's exact test) or the tetracycline group ($p = 0.13$, Fisher's exact test).

Complication risk increased with size of cyst in the tetracycline group (odds ratio 2.83, CI 1.31, 6.13, $p = 0.008$; score test for trend of odds) but not in the phenol group (odds ratio 1.46, CI 0.65, 3.26, $p = 0.36$; score test for trend of odds), despite the fact that larger volumes of sclerosant were used for larger cysts in the phenol group.

The number of injections required for cure was unrelated to size of the cyst in the tetracycline group (odds ratio 2.64, CI 0.76, 9.25, $p = 0.13$; score test of trend for odds) but increased as size increased in the phenol group (odds ratio 2.6, CI 1.21, 5.57, $p = 0.014$; score test of trend for odds), despite the fact that larger volumes of phenol were used for larger cysts.

DISCUSSION

The major shortcoming of historical comparison trials is that the groups may not be comparable. In this study, both groups had the same median age and mean cyst size (Table 2). There was no systematic refusal of treatment in either group so both groups were samples of consecutive patients presenting with scrotal cysts. Dropout rates are similar (Table 2) as are criteria for inclusion and exclusion, treatment procedure and assessment of results and all procedures and assessments were performed by one observer. Absence of control arms in both groups is another shortcoming of this study. The assumptions justifying absence of controls are that idiopathic vaginal hydroceles and epididymal cysts cannot be cured by simple aspiration and will have substantially re-accumulated within six weeks. The paucity of natural history studies and placebo control arms in sclerotherapy trials imply that other investi-gators assume the same thing. In the only study identified with a simple aspiration arm, Breda *et al* (13) noted a cure rate of 20% after simple aspiration of hydroceles.

Intention-to-treat analysis (effectiveness) yields cure rates of 76% for 5% phenol and 81% for tetracycline ($p = 0.54$, z-test of difference between proportions). Since per-protocol (efficacy) analysis yields cure rates of 100% for 5% phenol and 97% for tetracycline ($p = 0.26$, z-test of difference between proportions), the uncured cysts in the intention-to-treat analysis are almost completely accounted for by loss to follow-up or withdrawal. Some were withdrawn in the phenol study because of general ill-health. Only one patient in each group was lost to follow-up after experiencing mild pain on injection of sclerosant and none with severe pain in the tetracycline group was lost to follow-up, implying that pain was not a major deterrent. The most plausible reason for loss to follow-up is cure, with patients feeling that further follow-up was a waste of time (and money).

The 100% cure rate for 5% phenol and 97% for tetracycline from the per-protocol analysis confirm that treatment of idiopathic scrotal cysts with either sclerosant is reliably successful after 3 to 4 instillations. Others have also found phenol (8–10, 15, 16) and tetracycline (1, 4, 17) to be reliably curable after multiple instillations, although occasional refractory cases (requiring more than four instillations) occurred with 2.5% and 3% phenol (8–10).

Comparison of cure rates after one instillation of 5% phenol (70.5%) and tetracycline (88.6%) ($p = 0.052$, z-test of difference between proportions) favour borderline significant superiority of tetracycline (Table 2). This superiority disappears with two or more instillations (Table 2). Five per cent phenol gives significantly better results after one instillation in this study than 2.5% phenol in the studies of Savion *et al* (9) and Shan *et al* (10) but is not significantly better than 3% phenol in Ozdemir's study (8) at the 5% level (Table 3). The cure rate after one instillation of tetracycline in this study (88.6%) is similar to cure rates reported in several other studies (1–4, 6, 7) but significantly better than the 33.3% or lesser cure rates reported by others (12–14) (Table 4). The ineffectiveness of a single instillation of tetracycline reported by these latter three studies has been decisively disproved. Indeed, the cure rate after a single instillation of tetracycline may be even higher than 88.6% since at least two investigators have pointed out that delayed cures after initial re-accumulation are not uncommon (3,7). There should probably be a delay of 3 to 6 months before repeating treatment for re-accumulations of less than 100cc.

The severe pain experienced by some patients after tetracycline instillation has also been noted by others (1, 7, 11, 12, 14, 17). Cord block, which was highly successful in preventing pain in the tetracycline arm of this study, has also been recommended by others (1), as has dilution of the sclerosant in 1% lidocaine (7). Pain after phenol injection, though less severe, has also been noted by others (9,16). Certainly tetracycline sclerotherapy should not be performed without one of these pain prevention strategies.

The only potentially serious complication was encountered in the tetracycline arm of the study. One patient developed persistent testicular swelling after the third instillation and orchiectomy was performed, revealing a chronic haematocele. This complication should not be man-

aged by orchiectomy as a first resort. Unequivocal diagnosis is possible with ultrasound imaging and should be followed by either watchful waiting or a decortication type of surgical procedure. Bullock and Thurston (1) also reported orchiectomy for an infected haematocele after tetracycline instillation. Dahl (20) reported a case of gangrene of scrotum and penis after extravasation of tetracycline. This latter complication must be avoided by careful attention to technique.

Other complications aggregated (acute haematocele and thickening of scrotal contents) occurred equally in both groups at a rate of approximately 25% (Table 2) although acute haematocele requiring aspiration occurred only in the phenol group. Similar complications have also been noted by others for both phenol (16) and tetracycline (1). Since all cases settled completely over time, the clinical significance of these complications lie in the possibility that they may reflect a degree of inflammation and fibrosis severe enough to transgress the tunicas vaginalis and albuginea and involve the seminiferous tubules. It is the assumption that this possibility might translate into infertility which has led most investigators to restrict sclerotherapy (and certainly bilateral sclerotherapy) to men over 60 years old and younger men who have already realized their reproductive ambitions. This is a very difficult if not impossible hypothesis to test and at present there is no evidence that unilateral sclerotherapy causes infertility. Osegbe (21) claimed that tetracycline instillation caused a reduction in sperm count after unilateral instillation. However, analysis of his article revealed that all the men treated for hydrocele had abnormally low sperm counts before treatment, reflecting either selection bias in favour of secondary rather than idiopathic hydroceles or problems with the laboratory procedures for testing semen. His choice of controls was also inappropriate, being fertile men with no hydroceles rather than men with hydroceles treated by simple aspiration and tested by the same laboratory as treated cases. Tammela *et al* (22) found no change in the size or structure of testes on long term ultrasound follow-up of patients treated with ethanolamine oleate and Shan *et al* (10) found no alteration from pre-treatment levels in sperm concentration at six months and one year after phenol sclerotherapy. Restric-ting unilateral sclerotherapy to men who have realized their reproductive ambitions implies that surgery, the alternative option, is safe for men who want to preserve fertility but there is evidence to the contrary. Ross and Flom (23) re-ported three cases of infertility caused by hydrocelectomy and Zahalsky *et al* (24) reported finding segments of epidi-dymis in 5.62% of specimen after hydrocelectomy and 17.2% after spermatocelectomy and felt that patients should be informed of the risk of infertility from these surgical procedures. The same approach, of informed consent, should be utilized when presenting men with the option of sclerotherapy and it should not be implied that surgery is a safer treatment modality.

Another concern about sclerotherapy with chemicals which might transgress the tunicas vaginalis and albuginea must be genotoxicity, although this is not discussed in the literature. Both phenol and tetracycline have been used to treat various conditions in different parts of the body with no reports of genotoxicity but the presence of these chemicals in high concentration and proximity to the genetic apparatus should cause concern. Both phenol (25) and tetracycline (26) have been tested *in vitro* and found not to be significantly genotoxic in the absence of adjuvants.

In summary, both 5% phenol and tetracycline reliably achieve cure in sclerotherapy of idiopathic hydroceles and epididymal cysts after 1–4 and 1–3 injections respectively. Both are acceptable alternatives to surgical treatment. Cure rate after a single injection is significantly higher for tetracycline than 5% phenol but this advantage disappears after more than one injection. Cord block effectively prevents severe pain from tetracycline injection. Other complications aggregated (acute haematocele and swelling of scrotal contents) occur equally in both treatment arms although acute haematocele requiring aspiration occurred only in the phenol group. Concerns about fertility should be dealt with by obtaining informed consent rather than by offering surgery as a safer alternative, since surgery also poses a definite though unquantified threat to fertility.

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