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Comparison of polidocanol and tetracycline in the sclerotherapy of testicular hydrocele and epididymal cyst

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Objective To compare the effects and side-effects of polidocanol and tetracycline when used as sclerosants for testicular hydrocele and epididymal cyst.

Patients and methods Forty-five men (median age 67 years, range 42–81) with 46 hydroceles or epididymal cysts were assessed. After puncture and aspiration, the empty sac was instilled with either polidocanol or tetracycline, assigned randomly. Patients recorded any treatment-associated pain on a visual analogue scale.

Results At 9 months of follow-up, nine of 17 men were cured after sclerotherapy with polidocanol compared with 17 of 20 men treated with tetracycline ($P < 0.05$). Tetracycline produced some pain for 3 days after treatment while polidocanol therapy was almost pain-free. Re-instillation should be considered for recurrences. At the follow-up after 35 months, 16 of 18 men treated with polidocanol and 20 of 22 men treated with tetracycline were satisfied with the outcome.

Conclusion Both polidocanol and tetracycline are useful sclerosants for treating testicular hydrocele and epididymal cyst. We prefer polidocanol as a first choice in older patients because there were few short-term side-effects.

Keywords Hydrocele, epididymal cyst, sclerotherapy, tetracycline, polidocanol

Introduction

Radical surgery has been the standard treatment for testicular hydrocele and epididymal cyst [1,2]. Interest was shown in injection sclerotherapy after Moloney [3] concluded that sclerotherapy compared favourably with surgery in terms of efficacy and side-effects. During recent years, various sclerosing agents have been described in a series of phase II studies; effective treatment has been described using phenol [4], ethanolamine oleate [5], sodium tetradecyl sulphate [6], polidocanol [7] and tetracycline [8,9]. The side-effects are generally reported to be low, except for tetracycline, where the results are conflicting. Some authors [10] rejected the use of tetracycline because it produced frequent, severe scrotal pain after treatment, while others [11] reported pain as an occasional complication.

Few studies have compared different sclerosants [12]; thus the objectives of the present study were to compare effects and side-effects of polidocanol and tetracycline as sclerotherapy for testicular hydrocele and epididymal cyst.

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Patients and methods

Forty-five men (median age 67 years, range 42–81) with primary testicular hydrocele or epididymal cyst entered the trial. Patients with ipsilateral hernia, patent processus vaginalis, recent epididymitis or without transillumination at scrotal examination were excluded. Because polidocanol is an alcohol derivative, no patient took disulfiram. Some patients underwent scrotal ultrasonography pre-operatively.

All patients were treated on an out-patient basis according to a common protocol in three separate Departments between December 1991 and February 1994. Under sterile conditions, the sac was compressed to render it tense. The scrotal skin was not infiltrated with local anaesthetic. A 1.2 mm intravenous infusion needle with plastic cannula (Venflon®, Viggo, Sweden) was inserted into an area free of large blood vessels on the upper aspect of the fluid accumulation. The needle was withdrawn and the sac aspirated via the cannula connected to a three-way stopcock with extension tubing; an aliquot of the aspirated fluid was examined cytologically. An epididymal cyst was defined as accumulation of scrotal fluid containing spermatozoa at microscopy, while a testicular hydrocele contained no spermatozoa. The absence of blood staining in the aspirated fluid and unobstructed aspiration just before

the instillation of sclerosant were considered essential to ensure that the plastic cannula was within the sac during the installation of sclerosant. Either polidocanol (2 mL of 3% Aethoxysklerol®, Kreussler, Germany) or tetracycline (500 mg doxycycline, Vibramycin®, Pfizer in 2 mL of water) mixed with 5 mL of 2% lignocaine hydrochloride (Xylocain®, Astra, Sweden) was then instilled and the cannula withdrawn. Patients received tetracycline or polidocanol according to whether they were born on even or odd days, respectively. The dose of sclerosant was fixed and independent of the volume of fluid aspirated from the sac. One patient with bilateral testicular hydrocele was treated initially with polidocanol and contralaterally with tetracycline in a separate session. The characteristics of the two treatment groups are given in Table 1. None of the differences between the groups were statistically significant. A few minutes after the instillation of sclerosant, the patient's assessment of scrotal pain was recorded on a nominal scale by the urologist.

Follow-up

Patients were asked to record pain in the scrotum and groin on a visual analogue scale (VAS) from 0 (no pain) to 100 mm (worst possible pain) at between 14.00 and 18.00 hours on each of the 4 days after treatment [13]. All patients received a prescription of opioid analgesics (codeine phosphate 30 mg, paracetamol 400 mg) and were asked to record the total duration of pain and the associated use of painkillers; 22 pain-evaluation forms were returned in each of the groups. Patients were assessed after 3 and 9 (range 6–12) months and cure was defined as the absence of scrotal fluid at the clinical examination. Cases of symptomatic reaccumulation of fluid at follow-up were considered as recurrences and re-treated, the sclerotherapy being performed as it had been initially.

For the long-term evaluation, a questionnaire asking about persistent scrotal swelling, intercurrent treatment and satisfaction with the outcome of sclerotherapy was distributed a median of 35 (range 24–55) months after the initial treatment. Four patients, one treated with tetracycline and three with polidocanol, were no longer alive at the long-term follow-up. Two patients, both treated with polidocanol initially, had undergone scrotal surgery. All data obtained after open surgery were excluded from further analysis. In three cases, responses to the questionnaire were obtained by telephone interview. All the remaining patients returned the questionnaire.

Median values and quartiles within parentheses are given unless otherwise indicated. For the comparison between groups, the Mann-Whitney *U*-test or Fisher's exact test were used, with $P<0.05$ (two-tailed) considered to indicate statistically significant differences [14].

Results

The aspiration volumes in the two treatment groups are given in Table 1. Immediate pain after polidocanol treatment was reported by one of the patients and the instillation of tetracycline produced moderate or strong pain in 14 ($P<0.01$). After tetracycline instillation, eight of 10 men with hydrocele and six of 13 with epididymal cyst experienced pain immediately. On the day after instillation, 18 of 22 men had scrotal pain after receiving tetracycline and two of 22 reported pain after polidocanol ($P<0.01$). Over the 3 days after instillation, treatment with tetracycline induced more pain than did that with polidocanol (Table 2). The total use of painkillers in the group treated with tetracycline on each of the first four post-operative days was 41, 16, 11 and two tablets, respectively, whereas none were used after polidocanol sclerotherapy.

Three months after treatment with polidocanol, 12 of 22 men were cured and seven were re-treated after a second aspiration of 90 (60–140) mL of fluid. The volume of the initial aspiration of these re-treated men, 285 (145–360) mL, was not significantly different from initial aspiration volume of 183 (99–327) mL in the

Table 1 Characteristics of groups randomly allocated to treatment with polidocanol or tetracycline

	Tetracycline	*Polidocanol*
Number of patients	22	23
Age of patients (years) [Median (quartiles]	65 (57–69)	69 (62–76)
Aspiration volume (mL) [Median (quartiles]	210 (110–350)	190 (110–330)
Number of hydroceles	10	15
Number of epididymal cyst	13	8

Table 2 The degree of pain, as assessed using the VAS, after the instillation of either polidocanol (n = 22) or tetracycline (n = 22) for hydrocele or epididymal cyst

Days after instillation	*Polidocanol*	*Tetracycline*
	(median [quartiles])	
1	3 (2–4)	16 (3–77)*
2	2 (0–3)	15 (3–32)*
3	2 (0–3)	8 (2–21)*
4	2 (0–3)	3 (1–7)

* $P<0.01$ when compared with the polidocanol value.

remaining patients of the polidocanol group. After tetracycline sclerotherapy, 20 of 23 men were cured and none was re-treated. Nine months after the initial treatment, nine of 17 men were cured in the polidocanol group; three patients were re-treated, after the aspiration of 160 (132–202) mL, two of these having also been re-treated at the previous follow-up. After tetracycline sclerotherapy, 17 of 20 men were cured, one man being re-treated, with the aspiration of 90 mL of fluid; the number of patients cured after polidocanol and tetracycline therapy were significantly different ($P<0.05$) both at 3 and 9 months after primary treatment. Scrotal haematoma developed in one patient after polidocanol instillation; because resorption was delayed, the scrotum was explored and the haematoma debrided. No fever or infection occurred in any of the patients. In the long-term follow-up (35 months) there was no scrotal swelling in 13 of 18 men treated with polidocanol and 20 of 22 treated with tetracycline. Sixteen of the 18 patients treated with polidocanol and 20 of the 22 treated with tetracycline were satisfied with the outcome of the treatment.

Discussion

These results show that both polidocanol and tetracycline are useful agents for the sclerotherapy of hydrocele and epididymal cyst. The cure rate at 9 months with polidocanol for hydroceles and epididymal cysts compares with the results of Sigurdsson *et al.* [15], who reported cure rates of 67% in hydroceles and 46% in epididymal cysts at 14 months. Lund and Bartolin [7] reported a cure rate of 85% in hydroceles 12 months after treatment with polidocanol; differences in the selection of patients might explain these differences. However, in the long-term follow-up, about 90% of the patients were satisfied with the treatment. Several reports have shown that tetracycline is an effective sclerosant, with cure rates comparable with [9,16], or higher [17,18] than those in the present study. However, reports on pain after the injection of tetracycline are very variable, with incidences ranging from negligible to 85% [18,10]. The measurement of pain is difficult because it is a subjective personal psychological experience. Many investigators currently use VAS to obtain more objective and reproducible assessments [13]. As the published results on pain after tetracycline injection are variable, the present study focused on the estimation of pain; the VAS, combined with information on the use of painkillers after treatment, clearly suggests that sclerotherapy with tetracycline produced significant pain in most patients, in agreement with those who described pain as a significant problem after tetracycline treatment [17,19,20]. Interestingly, despite distressing short-term complications with tetracycline, most patients were satisfied with the treatment at the long-term follow-up. Furthermore, the present results suggest that tetracycline-induced pain is experienced more frequently from hydroceles than from epididymal cysts; this warrants further study. A mixture of tetracycline and lignocaine has been proposed to prevent the problem of treatment-associated pain [16]. The present results do not support this idea. An injection with local anaesthetic into the cord before treatment is probably a better proposal to decrease tetracycline-associated pain [19]. Treatment with polidocanol was almost pain-free in the present patients, as well as in others [15,21]. However, the only scrotal haematoma occurring in the present patients was after injection with polidocanol, possibly because the sclerosant was displaced into the peritesticular tissue. When the aspirated fluid is even slightly blood-stained, the sclerosant should not be instilled.

There is some concern about treating patients of reproductive age with sclerosants; Osegbe [22] reported that oxytetracycline caused oligospermia after sclerotherapy. On the other hand, testicular ultrasonography before and after sclerotherapy showed no changes in testicular structure and size [5]. While there is some indication that sclerotherapy might decrease fertility, it seems reasonable to exclude younger men from this treatment until more data are available. In these cases, surgery is the first-line therapy, the choice of operative technique being a matter of debate. Recent work, with which we agree, advocates Lord's procedure as the best method [23].

The present results suggest that tetracycline is more effective than polidocanol in inducing sclerosis of the scrotal sac. This difference, and the clear difference in induced pain, are difficult to explain while so little is known about the mechanisms of action of scrotal sclerotherapy. It is thought that inflammation is induced, with secondary fibrosis between the layers of the tunica, through lysis of the endothelial cells of the sac. Such an inflammatory response, with thickened membranes and fibrin deposits, has been reported during operation after failed sclerotherapy [17]. It is also possible that both agents work by the same mechanisms but the 'signal' for fibrosis is stronger with tetracycline; it is then reasonable to expect a greater effect of polidocanol with higher doses. Alternatively, the action of the two drugs may differ; the combined use of the agents, with smaller doses of tetracycline, would be a possibility worth exploring. Further progress within this field clearly awaits animal models.

The sclerotherapy of symptomatic hydroceles and epididymal cysts offers several advantages over surgery. Sclerotherapy gives good long-term results and is very acceptable to the patients; the treatment is simple, takes

place in the out-patient clinic, recovery is usually rapid, the costs are low and consequently, treatment is cost-effective.

In conclusion, polidocanol is preferable as the first choice in sclerotherapy for hydrocele and epididymal cyst, because it has few side-effects. Tetracycline is an effective sclerosant, but induces pain for a few days. Symptomatic recurrences should be re-treated with another instillation of sclerosant. Most patients were satisfied with the long-term outcome after both polidocanol and tetracycline. Surgery has a role as a first-line treatment in younger patients where fertility is important.

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