

The Use of Tetracycline as Sclerosing Agent in Renal Cyst Aspiration: A Systematic Review

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Objective: Percutaneous aspiration sclerotherapy is indicated for treatment of symptomatic renal cysts. The efficacy and safety of the different sclerosing agents have been sources of debate and disagreement. The purpose of this study was to assess the efficacy and safety of using tetracycline aspiration sclerotherapy in a systematic review of the literature.

Materials and Methods: A systematic search was conducted on the following electronic databases: Cochrane Central Register of Controlled Trials, EMBASE, PubMed and HERDIN (until November 2017). Studies of cyst volume reduction after tetracycline aspiration sclerotherapy were included for full text evaluation. The quality of the studies and the risk of bias were assessed independently by the authors, based on the Cochrane Handbook for Systematic Reviews of Interventions.

Results: Three studies were included for full-text assessment. They included 87 patients. Overall, risk of bias was high. Complete renal cyst disappearance ranged between 29%-100% after a follow-up period of 3-36 months. Partial success/ $>50\%$ renal cyst reduction ranged between 85.7%-100%. Complications were minor and self-limited, postoperative procedural pain occurred most frequently.

Conclusion: The authors found good results with respect to efficacy and safety after tetracycline aspiration sclerotherapy of renal cysts. However, due to high risk of bias in the included studies, definite conclusions regarding efficacy could not be drawn.

Key words: aspiration sclerotherapy, renal cysts, system review, tetracycline, volume reduction

Introduction

Renal cysts are the most common benign lesions in the adult kidney.¹ Majority of renal cysts are simple and asymptomatic.¹ They exist in at least 50% of the adult population.^{2,3} However, they are rare in the pediatric patients, with an incidence of 0.55%.⁴

Simple renal cysts usually remain untreated requiring intervention only when they cause symptoms or undergo a complication.^{4,5,6} Indications for treatment of renal cysts include compression of calyces leading to hydronephrosis,

infection, mechanical discomfort, deteriorating renal function and hypertension.^{7,8}

There are various methods of treatment of renal cysts. However, renal cyst aspiration remains to be one of the treatment modalities for renal cysts. Percutaneous drainage of simple renal cysts has several advantages since it is minimally invasive, well tolerated by the patients, does not require hospital admission, and is easily executed under ultrasound guidance. Percutaneous chemical sclerosis represents a relatively non-traumatic alternative therapy in case of large symptomatic renal cysts.³

A variety of sclerosing agents have been used before. Glucose, phenol, iophendylate, polidocanol, minocycline and pantopaque have been used in the past to prevent reformation of cyst.⁹ Currently, the most popular sclerosing agent is 95% alcohol.^{9,10}

Tetracycline is the choice of sclerosing agent in the institution. Tetracycline has been used for some time as a sclerosing agent for the treatment of hydrothorax, hydrocele of the testis and epididymal cysts.^{11,12} Its mechanism of action is the induced cellular infiltration with proliferation of fibroblasts, resulting in a local inflammation of the lumen of the cysts resulting in fibrosis and finally adhesions of the cavity wall.¹⁰ The combination of sclerosing action with long-standing local antibiotic prophylaxis gives tetracycline an advantage over other sclerosing agents.¹³ The absorption is decreased by the induced inflammatory reaction and hence the antibiotic activity is continuous for several days.¹³ Tetracycline also has a lower partition coefficient and therefore migrates with more difficulty across cell membranes thus causing less injury to tissues beyond injected surface.¹¹

A systematic review is essential for this study to provide further evidence with regards to the efficacy of using tetracycline as a sclerosing agent in renal cyst aspiration.

This systematic review aims to identify and assess the available literature in evaluating the efficacy and safety of using tetracycline as a sclerosing agent in renal cyst aspiration.

Materials and Methods

A systematic review of relevant literature assessing efficacy of tetracycline as a sclerosing agent for renal cyst aspiration was conducted using electronic and manual searches. The search was done of the following databases: The Cochrane Central Register of Controlled Trials, EMBASE, PubMed, and HERDIN. The search terms included tetracycline and renal cyst. Reference lists were identified and hand-searching of related journals and abstracts were done. Two reviewers independently assessed the titles and abstracts identified by the search strategy. The full texts of

all potentially relevant studies were retrieved and evaluated independently by two reviewers and all studies that met all inclusion criteria were included in the review.

Trials were considered eligible if they met the selection criteria set prior to this review. The criteria included randomized controlled trials and case control studies with study population consisting of patients with renal cyst undergoing renal cyst aspiration using tetracycline as the sclerosing agent. Studies should have used tetracycline alone versus no sclerosing agent. Study design criteria for inclusion in this review were published randomized control trials and descriptive studies written in English with any level of blinding and containing any number of individuals of whom at least 80% were followed up.

The primary outcome measures considered for the review included cyst volume reduction on follow-up via imaging and safety profiles.

The quality of the studies and the risk of bias were assessed independently by the authors, based on the Cochrane Handbook for Systematic Reviews of Interventions. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting were checked for each study. Based on how the criteria were met, the methodological quality was classified into high (all criteria with low risk of bias), moderate (with one or more criteria with unclear risk of bias), and low (with one or more criteria with high risk of bias).

Results

Results of the Search

The initial search produced 10 possible titles . Three studies were assessed to be potentially eligible based on the abstract. Review of the full text reports yielded 3 eligible studies. Two studies were not randomized control trial.

Risk of Bias and Quality Assessment

One prospective study and two retrospective case series were included in this study. Overall, there was a high risk of bias for the prospective study. It was also not a fully paired comparative study of renal cyst aspiration versus renal cyst aspiration with tetracycline. The clinical setting of renal cyst aspiration was heterogeneous across studies.

Description of Included Studies

One randomized controlled study and two case series studies were included in the review. The studies were published between 1989 and 2007. Three studies with a total of 87 patients comprised the evidence for this review.

Patient population in the three studies included pediatric to adult patients (neonate to 85 years old) who underwent renal cyst aspiration with sclerotherapy. Cyst recurrence and/or cyst volume reduction was observed. The presence of adverse effects and occurrence of complications were reported.

In the randomized control study by Kilinc, et al. the patients were randomized into two groups: renal cyst aspiration alone (control group) and renal cyst aspiration + tetracycline sclerotherapy (treatment group). Initially, twenty patients were randomized into both groups. However, during treatment, they recognized better cyst volume reduction with the treatment group. Hence, they decided that it was not ethical to continue with renal cyst aspiration alone; all succeeding patients were then recruited into the treatment group. No blinding was done. Only minor complications were noted, with postoperative pain being the most common (26%).

In the case series by Reiner, et al., a total of four pediatric patients were treated with renal cyst aspiration with tetracycline sclerotherapy. All patients had disappearance of the cyst on repeat ultrasound after 6-34 months. Complications/side effects were not reported.

In the case series by van der Ent, et al., a total of seven patients (52-85) underwent renal cyst aspiration with tetracycline sclerotherapy. Two patients showed complete disappearance of the

cysts while five patients showed more than 50% cyst volume reduction. No complications were noted.

Discussion

A number of studies have demonstrated that simple renal cyst aspiration leads to a high recurrence rate in up to 80% of cases, therefore this is not considered an effective therapeutic approach.^{1,2,3,4,5} To reduce such recurrence rates, studies have shown success with renal cyst aspiration with concurrent percutaneous sclerotherapy with a variety of substances such as ethanol, lipiodol, povidone iodine, acetic acid, minocycline and tetracycline.^{1,2,3,4,6,8,10}

The various sclerosants have been used to provoke inflammation and adhesion of the cyst wall thus preventing recurrence. To choose the most effective agent with the least complications, several factors must be considered: toxicity, adverse systemic and local effects, secondary infection, availability and cost-effectiveness.

Tetracycline, which is a readily available antibiotic prepared from cultures of *Streptomyces* sp., is also used in other clinical settings: creating pleurodesis in the control of malignant pleural effusion or hydrothorax in continuous ambulatory peritoneal dialysis, in treating cysts of the thyroid gland, management of the cardiac tamponade secondary to malignant pericardial effusion, and in the treatment of hydrocele.⁹ Local antibiotic prophylaxis during these procedures gives tetracycline an additional advantage and is thus considered safer than other sclerosants.

Percutaneous sclerotherapy is a minimally invasive procedure, and is currently considered as one of the main options for the management of symptomatic renal cysts.

As to qualifying treatment success for renal cyst aspiration, several authors consider that: a) complete success corresponds to symptoms regression and cyst disappearance; b) partial success corresponds to symptoms regression and cyst persistence with < 50% of its original volume; c) treatment failure corresponds to symptoms persistence and cyst recurrence with > 50% of its original volume. In the literature, the complete

success rate for sclerotherapy ranges between 70% and 90%^{1,2,3,9}, with better results noted for smaller cysts.^{9,10}

In the studies included in this review, complete success/cyst disappearance was seen in 29%-100% of patients who underwent sclerotherapy with tetracycline. Partial success/>50% cyst volume reduction was seen in 85.7%-100% of patients. Treatment failure was seen in 0 - 4.7%.

The quality of data, however, is low-with two of the studies included being case series and the lone randomized control study has allocation concealment bias, is non-blinded and has incomplete randomization. There was also heterogeneity in the concentration of tetracycline sclerosant used among the studies.

Studies have shown that complications resulting from the procedure rarely occur and generally are self-limited. Most frequent complications are fever, pain, hematuria and small perinephric hematomas.^{1,12,13,17,18} The studies included in this review supported such results, with most complications being self-limited and no further interventions were required. The most common complications were postoperative pain and nausea.

Improving the quality of the evidence on percutaneous tetracycline sclerotherapy use is crucial to better define the role of this procedure in the management of renal cysts. The current evidence in this field is limited by several factors. First, most studies are observational studies, have relatively small sample sizes, and have heterogeneous populations. Secondly, the duration of follow-up was also relatively short for most of the studies, and this confers uncertainty regarding actual recurrence rates. Lastly, the studies have not employed a standardized tetracycline preparation.

Conclusion

Tetracycline sclerosant use confers moderate complete success (cyst disappearance) and excellent partial success (>50% cyst volume loss) and is associated with minimal self-limited complications. However, the quality of the available evidence is low, and well-designed

prospective cohort studies are required to verify these findings and address knowledge gaps.

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