

LETTER TO THE EDITOR

MINOCYCLINE HYDROCHLORIDE *VERSUS* TRIAMCINOLONE ACETONIDE AS MINI-INVASIVE TREATMENT IN SYMPTOMATIC BAKER CYSTS: A PROSPECTIVE STUDY

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To the Editor,

Popliteal cyst, also known as Baker's cyst (BC), is a fluid synovial lesion of the postero-medial part of the knee (1). It represents a distention of the gastrocnemio-semimembranosus bursa which communicates with the knee joint through a small capsular opening. The key pathogenetic role is played by a valve-type structure that allows unidirectional flow into the bursa (1). In 94% of cases BCs are secondary to intra-articular diseases: osteoarthritis, medial meniscal tear, ligament and chondral lesions (1), and inflammatory diseases (rheumatoid arthritis, seronegative and pyrophosphate arthropathy) (2). BC is often an accidental finding. Symptomatic BC typically presents with fullness and swelling (1). When the cyst breaks, it manifests with acute pain, itching and ecchymosis ("pseudothrombophlebitis syndrome") (3). Ultrasound (US) should be the first line examination as it has a very high sensitivity, but it cannot adequately visualize joint diseases (4). Magnetic resonance imaging (MRI) remains the reference standard method for the characterization of knee masses and the detection of related intra-articular pathologies (4) (Fig. 1). There are several therapeutic options: the traditional approach is to "watch and wait", while treating the underlying

joint disease. Surgical and arthroscopic techniques are described in literature but both have risks associated with the presence of vessels and nerves in the popliteal region (4). US-guided non-invasive procedures are therefore catching on, with aspiration of fluid and injection of drugs aimed to avoid cyst recurrence. Intra-articular or intra-cyst corticosteroid injection is a relatively low-risk and successful procedure in patients with knee osteoarthritis (5-7). A plethora of sclerosing agents are reported in literature: ethanol, phenol, lyophilized mixture of group A *Streptococcus pyogenes*, 12.5% dextrose and morrhuate sodium and fibrin glue have all been used to sclerose para-articular cystic cavities (8-11). We prospectively compare two therapy cohorts: antibiotic (minocycline hydrochloride) and steroid (Triamcinolone acetonide).

MATERIALS AND METHODS

We performed a prospective cohort non-randomized study, enrolling 80 patients [55 men, 25 women, mean age = 63 years (44 to 73)], affected by symptomatic BCs between 2017 and 2018. All patients had low to moderate knee pain while walking, and lamented sensation of weight and fullness ("mass effect") in the knee (Table

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I). Before treatment all patients underwent an orthopedic visit to confirm that the symptoms were due to the cyst enlargement. All patients were studied with US (64) or MRI (16), both performed by a radiologist with over 10 years of experience in musculoskeletal radiology. Fourteen patients were excluded because affected by a small cyst (less than 2 cm) and other comorbidities possibly responsible for the symptoms (rheumatoid arthritis, previous traumas, severe arthrosis). Eight patients did not complete the scheduled follow-up and were not included in the final analysis. The 58 patients included in the statistical analysis were allocated without randomization for each treatment: 30 treated with cyst drainage and injection with minocycline hydrochloride [16 women, 14 men, mean age of 65yrs (48 to 79)]; 28 treated with drainage and injection with tacetonide [16 women, 12 men, mean age: 62 years (44 to 76)]. Treatment did not require any hospitalizations or one-day-care at the hospital, but only a simple ambulatory radiologic consult. Patients presented to our Hospital with radiological exams (if not performed in our center). All procedures were conducted with US guidance with the only nurse assistance.

After the skin disinfection and, where appropriate, local anesthesia (performed according to the patient's compliance with 5 ml of Lidocaine 2%), the best puncture

site was selected with US. In most cases a fine needle (19G, length of 10 cm) was used, being atraumatic. In selected cases (3 patients) a bigger needle was used due to the high density of the cyst content. The US monitoring was continuous in order to spot the possibility of intracyst bleeding and the correct emptying of the fluid collection.

Patients treated with mynocicline hydrochloride, after emptying the cyst, were injected with a solution containing a dose of 3 mg of sclerotizing antibiotic per mL of drained fluid from the native cyst (for example a 20 mL cyst was treated with 60 mg of Mynocicline hydrochloride), dissolved in 3-5 ml (depending on the total quantity of drug injected) of saline water (Fig. 2 A and B).

Before treatment, the cyst volume was calculated with the ellipsoid volume formula ("length" × "width" × "depth" × 0.5233). Any pre- or post-treatment antibiotics were administered, and the only advice given was to rest after the procedure (avoiding intense physical activities) for at least 24 h. Minocycline hydrochloride was not drained after the injection but left in place inside the cyst.

In the Triamcinolone acetonide cohort (Triacort 40 mg), after completely emptying the cyst, 1 mL of drug (40 mg) was injected. In this cohort of patients the only advice given was to rest for the first 24 hours after the procedure. Observation after the procedure was 1 hour, checking for

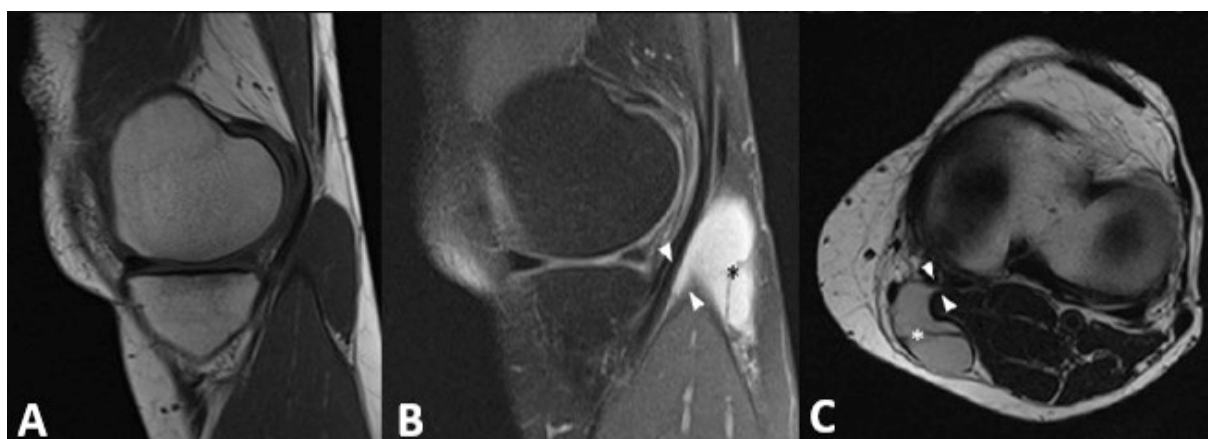


Fig. 1. MRI sagittal spin echo-T1w (A), turbo spin echo-T2w Fat Sat (B) and axial turbo spin echo-T2w (C) images. Large ovular formation, which extends from the knee posteriorly between the tendons of the medial head of the gastrocnemius and the semimembranosus, with low signal in T1w sequences and high signal in T2w, consisting in complicated Baker's cyst. Note the internal irregular septa (*) and the collar of the cyst (between the arrowheads) through which it is in communication with the joint cavity.

side effects described in literature such as hypersensitivity to the active agent and/or other ingredients, moderate pain or drug leakage.

The study design included a clinical follow-up (for cases with recurring symptoms) and a radiological follow-up (persistence or recurrence of cyst formation) through US exam, the results of which were analyzed at 6 months after the treatment. Our primary end-point was a volume reduction of 40% or more than the initial volume 6 months after therapy.

Secondary end points evaluated were: VAS score reduction after treatment confronted with the initial score, cyst persistence, considered as a volume reduction $<40\%$; and procedure duration: considering that all procedures, in both cohorts, were performed by the same radiologist.

This study was conducted according to the principles expressed in the Declaration of Helsinki. The trial protocol was approved by the ethics committee of Novara. All patients provided written informed consent for the collection of data and subsequent analysis.

Statistical analysis

For the purpose of the study we considered only patients fulfilling the overmentioned inclusion criteria. Data were analyzed using StataMP version 13.0 Windows. Patient

samples were statistically analyzed at time 0, to assess the homogeneity of the sampled data and in order to find the comparable variables between the two samples. We outlined the following statistically significant variables, defined by the primary and secondary endpoints:

- treatment type/volume variability of the cyst, from t0 to t1.
- treatment type/VAS
- treatment type/number of recurrences.

Each quantitative variable was described as mean value and standard deviation. We used qualitative variables, frequency and percentages.

Statistical analysis was employed to compare the results of treatment with cortisone versus minocycline over Baker's cysts. Statistical analysis was performed with Student's *t*-test, and/or Wilcoxon test to analyze continuous variables, *chi*-squared test or Fisher exact test for dichotomous variables and categorical variables and F test for variance analysis. Significance was attributed to values <0.05 .

RESULTS

The results of this prospective study were analyzed after a clinical and radiological follow-up at 6 months after the procedure for each patient (Jan 2018 to April 2019). We excluded 8 patients who

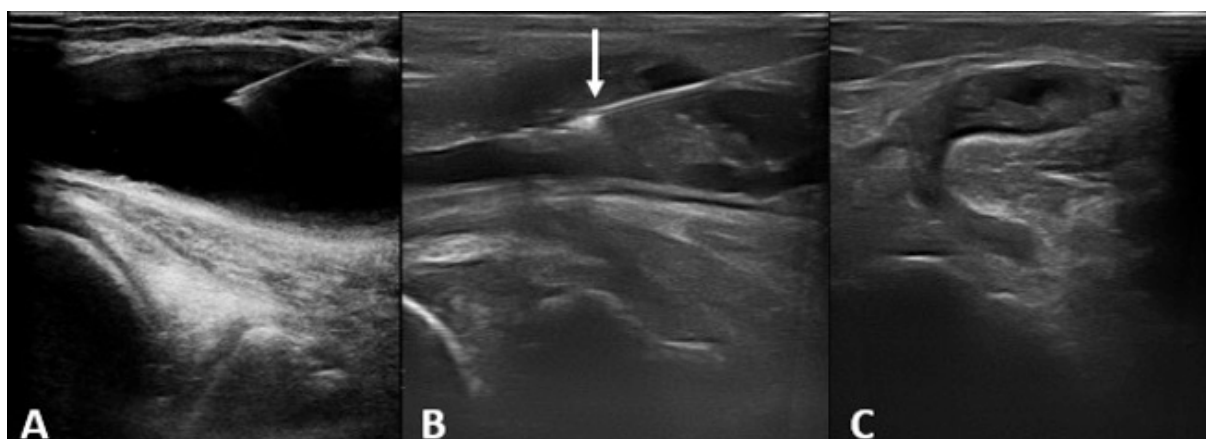


Fig. 2. US Sagittal image of the postero-medial knee region shows a large simple Baker's cyst (A). Puncture of the Baker's cyst with standard length spinal needle (arrow) under real time US-guidance, fluid aspiration and injection of Minocycline (B). US control study after 6 months shows complete resolution with negligible residual fluid and thickened walls (C).

refused follow-up control. Some cases demonstrated persistence/recurrence of disease shortly after therapy: some of them were re-treated (3 from the antibiotic group, 2 from the steroid group), with good results, whereas some of them (2 from the antibiotic group, 1 from the steroid group) were not treated because of patient's decision or adjoining diseases. Final analysis shows two cohorts of patients with BCs, 30 of whom were treated with drainage and Minocycline hydrochloride infusion, and 28 treated with drainage and Triamcinolone acetone injection. The procedure was well tolerated in all patients and no need of local anesthetic was necessary (except for 3 patients). During puncture and aspiration and post-procedure period no complications were documented.

In patients treated with Minocycline hydrochloride infusion, the primary endpoint (cyst volume reduction equal or >40% compared to initial volume) was obtained in 66.7% of cases with a mean reduction of volume up to 54% (Fig. 2C). In patients treated with Triamcinolone Acetonide, however, the primary endpoint was obtained in 35% of cases, in whom the reduction of volume reached 69%. Analysis of data showed a statistically significant volume reduction with therapy.

The secondary endpoint analysis showed a global reduction of VAS after treatment (with both antibiotic and cortisone) with a mean of 3.2 points. In patients treated with Minocycline hydrochloride, VAS reduction reached 3.3 as a mean, while patients treated with Triamcinolone acetone reached

Table I. Population distribution.

| Population | | Minocycline cloridrate Tot. 30 (51.7%) | Triamcinolone acetone Tot.28 (48.3%) | p* |
|------------|---------------------------------------|--|--|--------|
| Age | <50 | 4 (13.3%) | 6 (21.4%) | 0.312 |
| | 50-59 | 9 (30.0%) | 7 (25.0%) | |
| | 60-69 | 11 (36.7%) | 5 (17.9%) | |
| | >70 | 6 (20.0%) | 10 (35.7%) | |
| Gender | Female | 16 (53.3%) | 16 (57.1%) | 0.798 |
| | Male | 14 (46.7%) | 12 (42.9%) | |
| Local | Right | 16 | 15 | 1 |
| | Left | 14 | 13 | |
| VAS score | <3 | 12 (40.0%) | 3 (10.7%) | <0.05* |
| | 3 4 5 | 7 (23.3%) | 15 (53.6%) | |
| | >5 | 11 (36.7%) | 10 (35.7%) | |
| Symptoms | Discomfort | 10 (33.3%) | 1 (3.5%) | <0.05* |
| | Physical limitation | 4 (13.3%) | 8 (28.6%) | |
| | Mild Pain | 4 (13.3%) | 0 (0.0%) | |
| | Moderate Pain | 0 (0.0%) | 0 (0.0%) | |
| | Pain at rest | 0 (0.0%) | 4 (14.3%) | |
| | Physical limitation and mild pain | 6 (20.0%) | 4 (14.3%) | |
| | Physical limitation and moderate pain | 4 (13.3%) | 8 (28.6%) | |
| | Physical limitation and pain at rest | 2 (6.8%) | 4 (14.3%) | |

* $p < 0.05$

3.1 VAS reduction. No statistically significant difference was found between the two methods as far as VAS was concerned. Analysis of persistence/recurrence of the disease after treatment was 33.3% in cases treated with Minocycline hydrochloride *versus* 64.3% in patients treated with Triamcinolone acetonide (Table II).

The last endpoint was procedural time, which showed a significantly longer duration [up to a mean of 15.5 min (12.9 to 18.1)] with Minocycline hydrochloride treatment compared to a mean of 8.6 min. (7.7 to 9.5) for the Triamcinolone acetonide treatment.

No major or minor complications were found in either cohort. More specifically, there was no local bleeding or pain during the procedure.

DISCUSSION

Besides the variability of therapeutic approaches (surgical or non-invasive), BC recurrence is a common event. It is important to establish a safe and easily reproducible therapeutic regimen. Previous retrospective studies or case reports demonstrated the efficacy of treatment with drainage and US-guided steroid or sclerosing agent injection (5-11). Short-term efficacy was evident from a clinical point of view (good results achieved the first few weeks after treatment), but the recurrence rate was high.

This is the first prospective study that compares a group submitted to aspiration and steroid injection (Triamcinolone acetonide 40 mg) to a group submitted to drainage and an antibiotic injection

Table II. Relapses and VAS score analysis in both cohorts of atients treated with Minociclyne and steroid.

| Population | | Relapse Tot. 28 (48.3%) | NO Relapse Tot.30 (51.7%) | p* |
|------------|---------------------------------------|----------------------------|------------------------------|--------|
| Age | <50 | 8 (28.6%) | 2 (6.6%) | 0.798 |
| | 50-59 | 5 (17.9%) | 11 (36.7%) | |
| | 60-69 | 8 (28.6%) | 8 (26.7%) | |
| | >70 | 7 (25.0%) | 9 (30.0%) | |
| Gender | Female | 14 (50.0%) | 18 (60.0%) | 0.598 |
| | Male | 14 (50.0%) | 12 (40.0%) | |
| Local | Right | 17 (60.7%) | 14 (46.7%) | 0.306 |
| | Left | 11 (39.3%) | 16 (53.3%) | |
| VAS score | <3 | 6 (21.4%) | 9 (30.0%) | 0.798 |
| | 3 4 5 | 11 (39.3%) | 11 (36.7%) | |
| | >5 | 11 (39.3%) | 10 (33.3%) | |
| Symptoms | Discomfort | 2 (7.1%) | 9 (30.0%) | <0.05* |
| | Physical limitation | 4 (14.3%) | 8 (26.7%) | |
| | Mild Pain | 1 (3.5%) | 3 (10.0%) | |
| | Moderate Pain | 0 (0.0%) | 0 (0.0%) | |
| | Pain at rest | 3 (10.7%) | 1 (3.3%) | |
| | Physical limitation and mild pain | 7 (25.0%) | 3 (10.0%) | |
| | Physical limitation and moderate pain | 5 (17.9%) | 6 (20.0%) | |
| | Physical limitation and pain at rest | 6 (21.4%) | 0 (0.0%) | |

* $p < 0.05$

(Minocycline hydrochloride, a tetracycline family antibiotic). Minocycline hydrochloride is used as a sclerotizing agent, since its low Ph is active on endothelial cells covering the inside layer of the cyst, avoiding recurrence, especially when there is a coexistence of inflammatory joint diseases. The latter treatment has already been used in hepatic and renal cysts, showing better efficacy regarding recurrence and a better safety profile compared to alcohol, as a sclerotizing agent (12).

In our study both drugs showed an excellent safety profile (there were no major or minor complications) and efficacy in reducing the volume of cysts. Despite a longer procedural time, Minocycline hydrochloride treatment was more effective than Triamcinolone acetonide, because of a minor number of cases experiencing disease persistence or recurrence. It is unclear why in some patients the treatment is not effective: some Authors hypothesized that the presence of septal formations block the drug's diffusion; another possible cause for inefficacy might be explained by the presence of a wide communication between the cyst and the articular cavity, which may reduce the drug concentration in the cyst itself, spreading to the knee cavity. In conclusion, percutaneous sclerosis with Minocycline hydrochloride should be considered a very effective and promising non-surgical treatment for symptomatic BC.

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