Percutaneous Sclerotherapy of Renal Cysts with a Beta-Emitting Radionuclide, Holmium-166-chitosan Complex

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Objective: To evaluate the usefulness of a beta-emitting radionuclide (holmium-166-chitosan complex) as a sclerosing agent for the treatment of renal cysts.

Materials and Methods: Using 10–30 mCi of holmium-166-chitosan complex, 20 renal cysts in 17 patients (14 male and 3 female patients, ranging in age from 47 to 82 years) were treated by percutaneous sclerotherapy under ultrasonographic guidance. The volume of the cysts before and after the sclerotherapy and the percentage change in volume were calculated in order to evaluate the response to therapy, which was classified as either complete regression (invisible), nearly complete regression (< 15 volume% of initial volume), partial regression (15–50 volume%) or no regression (> 50 volume%).

Results: The follow-up period ranged from 6 to 36 months (mean 28 months). Eighteen cysts (90%) regressed completely (n=11, 55%) or near-completely (n=7, 35%). Partial regression was obtained in one patient (5%) and there was no regression in one patient (5%). No significant complications were encountered.

Conclusion: The holmium-166-chitosan complex seems to be useful as a new painless sclerosing agent for the treatment of renal cysts with no significant complications.

Index terms:
Kidney, cystic
Sclerotherapy
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Renal cysts are very common abnormalities, particularly in the aging adult population. The incidence of cysts in the population over the 6th decade is as much as 50%, and the cyst size also increases with age (1–3). In the majority of cases, the cysts remain asymptomatic and usually require no invasive treatment. Occasionally, however, some cysts may cause pain, hematuria or a non-specific gastrointestinal manifestation such as nausea. There are rare incidences where renal cysts induce infection, hypertension, obstruction of the proximal urinary tract and even renal failure in some complicated cases (4–8).

Simple aspiration and sclerotherapy are minimally invasive procedures, and ethanol therapy had been widely used for the treatment of symptomatic renal cysts (9–11). The ideal sclerosing agent should be safe, painless during the procedure, have no significant side effects and minimize recurrence. However, various ethanol-related complications have been noted such as pain, fever and systemic reactions such as drunken state or shock; moreover, the recurrence rate has been reported to be 32% after a single-session alcohol sclerotherapy (11).

To overcome the drawbacks associated with the use of alcohol as a sclerosing agent, various other sclerosing agents have been employed for the complete single-session ablation of renal cysts, but no satisfactory long-term results have yet been documented (12–16). There have been several encouraging reports on the use of low-energy

electron-emitting radionuclides in the local radiation treatment of small tumors and in radionuclide synovectomy (17−25). To the best of our knowledge, however, so far there have been no reports which described the successful use of radionuclides for the ablation therapy of renal cysts. The purpose of this study was to evaluate the ability of a beta-emitting radionuclide (holmium-166-chitosan complex) to act as a sclerosing agent for the treatment of renal cysts.

MATERIALS AND METHODS

From March 2001 to February 2002, seventeen patients underwent sclerosing therapy for renal cysts. There were 14 men and 3 women (mean age, 67 years; age range, 47−82 years). The indications for treatment were as follows: a cyst larger than 5 cm in diameter (large cyst) that increased in size during follow-up (n=10), a cyst with flank pain (n=3), a cyst with hematuria (n=2), a large cyst with impending rupture due to an adjacent abdominal aneurysm (n=1) and the failure of previous ethanol sclerotherapy (n=1). Informed consent was obtained from all of the patients and all examinations were performed in accordance with the recommendations of our institutional review board.

Holmium solution ($^{166}Ho(NO_3)_3 \cdot 5H_2O$) was generated at the Korea Atomic Energy Research Institute (Taejon, Korea) and we used the holmium-166-chitosan complex in this study. Chitosan is a polymer of 2-deoxy-2amino-D-glucose with β1, 4 bonds that is derived from the deacetylation of chitin. It was supplied by a Pharmaceutical Development Laboratory (Dong Wha Pharm. Ind. Co., Ltd., Kyunggi-do, Korea).

A total of 20 renal cysts were included in this study. They were evaluated by ultrasonography and, in each case, the volume of the cyst was calculated using the method described by Pedersen et al. (26), i.e.,

$$Volume = \pi(l \times w \times d) / \sigma$$

[l; length, w; width, d; depth of the cyst]

Under ultrasonographic guidance, an 18−21 G puncture needle was placed in the cyst, and as much as possible of the cystic fluid was gently aspirated. Depending on the volume of the cyst, 10−30 mCi (1−2 ml) of holmium-166-chitosan complex was administered through the puncture needle; 10 mCi for cysts < 100 ml, 20 mCi for cysts from 100 to 150 ml and 30 mCi for cysts > 150 ml. After the procedure, gamma camera imaging was performed to verify whether any leakage occurred.

Serial follow-up ultrasonography and a complete blood count and urine analysis were performed for a period of 6−36 months: where possible, these tests were scheduled at 1−2 month(s) and 6, 12 and 18 months. The volume of the cysts before and after the sclerotherapy and the percentage volume change were calculated, in order to evaluate the response to therapy. The treatment effects were classified as complete regression (invisible), nearly complete regression (< 15 volume% of the initial volume), partial regression (15−50 volume% of the initial volume), and no regression (> 50 volume% of the initial volume).

RESULTS

The calculated volume of the cysts before sclerotherapy ranged from 16 to 258 ml, with a mean volume of 90 ml. Aspirated fluids from all cysts were clear transudates with no microscopically detected presence of malignant or atypical cells. Upon gamma camera examination, the radioactivity was found to be localized at the site of administration in all patients, without any distribution to the other organs or tissues.

The mean follow-up period was 28 months (6−36 months). At the initial follow-up after 1−2 month(s), the mean volume of the remaining cysts was 33% of the initial volume. At the 6-month follow-up, the mean volume decreased to 15% of the initial volume. At the 12-month follow-up, the mean volume further decreased to 10% of the initial volume. At the final follow-up, the mean residual volume was 8% of the initial volume. Eighteen cysts (90%) were completely (n=11, 55%) or nearly completely (n=7, 35%) regressed (Figs. 1, 2). Partial regression was obtained in 5% of cases (n=1) and there was no regression in one patient (5%) (Table 1). An organizing hematoma developed in one patient, and this seems to have been the reason for the absence of regression of the cyst in this patient.

No patients complained of any significant pain during the procedure. No significant complications were encountered during or after the procedure, other than in the case of one patient who showed a mild fever for three days without leukocytosis, and in whom the fever subsided without treatment. There were no remarkable findings on the follow-up complete blood counts and urine analyses and there were no further complaints about flank pain.

DISCUSSION

Management of symptomatic renal cysts can be accomplished by several methods. Surgical resection is still the treatment of choice for renal cysts. Recently, laparoscopic decortication or marsupialization of simple renal

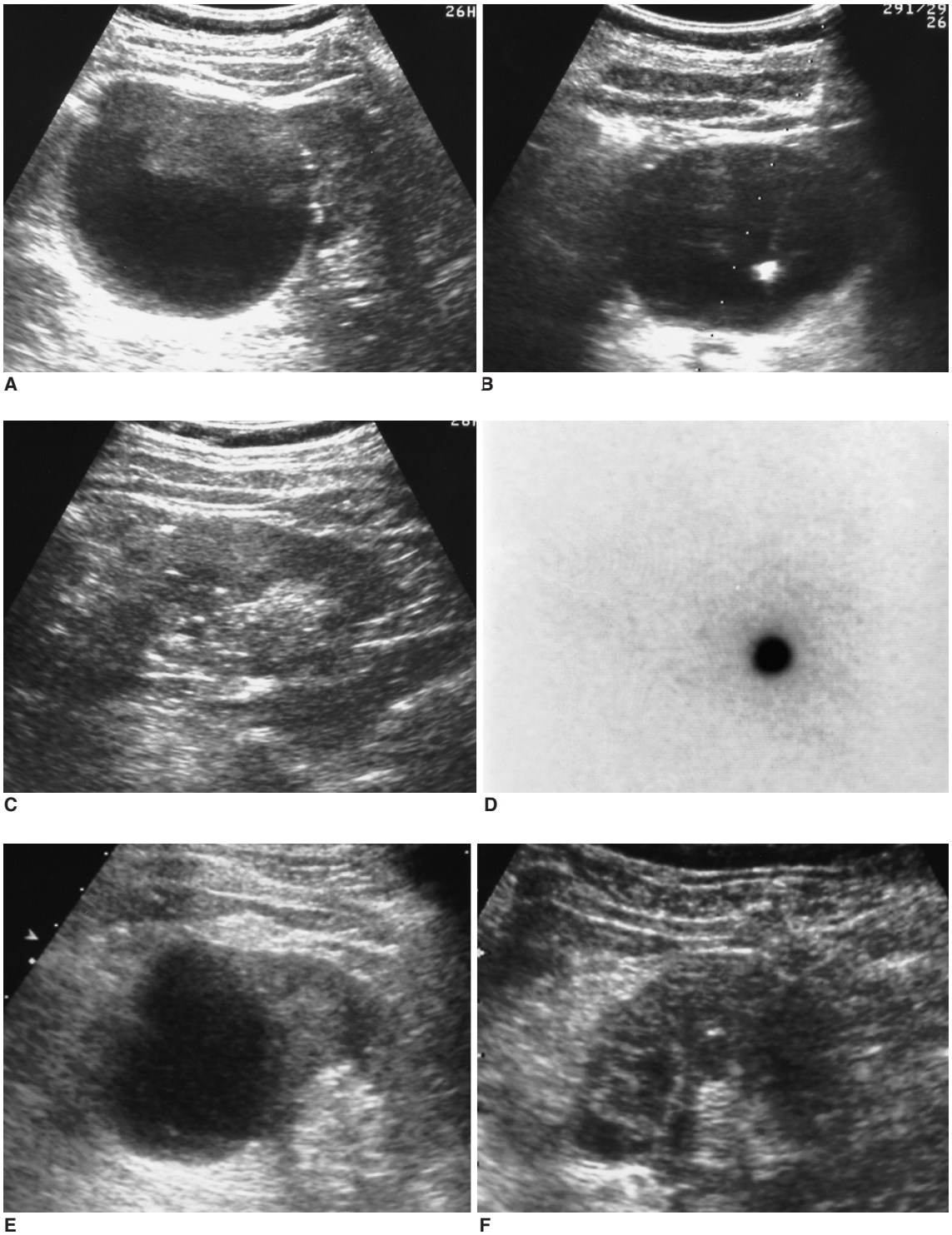


Fig. 1. A 57-year-old man with right flank discomfort.
A. Sonography of the left kidney demonstrated a giant simple cyst. The initial volume was 172 ml.
B, C. Under sonographic guidance, an 18 G puncture needle was placed in the cyst (**B**) and as much as possible of the cystic fluid was gently aspirated. 30 mCi of holmium-166 chitosan complex was administered at the site of the placed puncture needle (**C**).
D. Gamma camera image (coronal anterior view) showed the focal accumulation of radioactivity without any evidence of leakage.
E. On the sonogram 1 month after the procedure, the cyst was found to have decreased to a volume of 47 ml.
F. The cyst disappeared at follow-up sonography 6 months after the procedure.

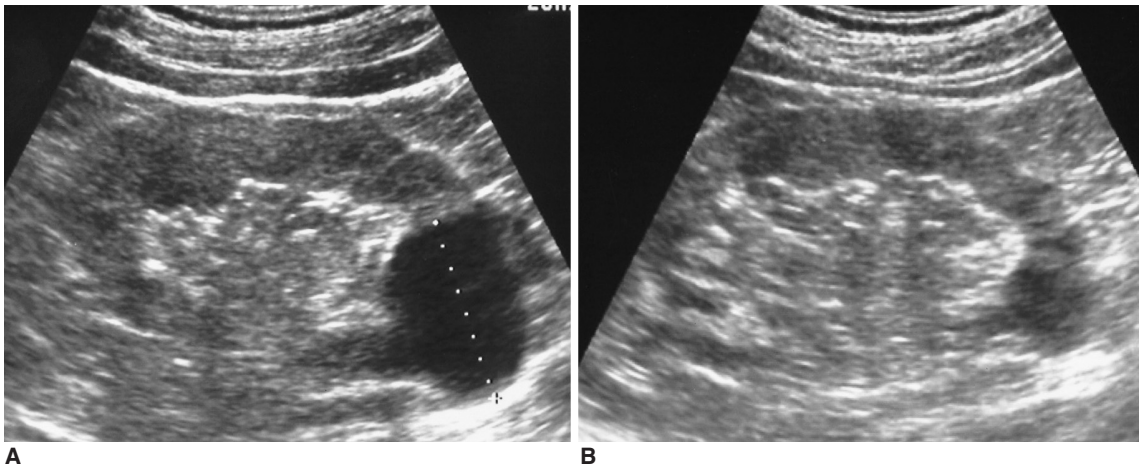
cysts was introduced to reduce the procedure related morbidity (27–30). However, both modalities are invasive, requiring general anesthesia with the accompanying operative morbidity and complications that this brings. Thus, they have been replaced by minimally invasive approaches that are based on percutaneous needle aspiration or sclerotherapy (9).

Aspiration of renal cysts under ultrasonographic or CT guidance has previously been performed for diagnosis and treatment, but renal cysts treated by simple aspiration frequently recur because the secretory epithelial lining remains. In such cases, the recurrence rate after 2 years was reported to be as high as 80% (11). Many sclerosing agents have been used to destroy the secretory epithelium and so prevent cyst recurrence following aspiration. Ethanol has generally been viewed as a safe and effective sclerosing agent, and it has shown good initial results. However, ethanol use is associated with various complications, including pain, fever and systemic reactions, such as drunkenness and shock. In addition, its effectiveness is reduced by dilution from the remaining cystic fluid and the recurrence rate after a single-session of sclerotherapy has been reported to be as high as 32% at the 2-year follow-up (11).

Direct intratumoral injection of high-energy beta-emitting radionuclides has been introduced as a potential alternative to systemic targeted therapy for the local control of solid tumors. Holium-166 attached to diverse carriers has been used effectively not only in radionuclide synovectomy (17, 18), but also in the treatment of solid hepatic tumors (19–22) and for the treatment of skin cancer (23, 24). Holmium-166 may also be appropriate for the radionuclide sclerotherapy of renal cysts: it has a relatively short half-life of 26.83 hours, a short penetration range of 2.3mm, a high beta-energy (1.85 MeV) and a low

Table 1. Summary of Therapeutic Responses

Response to Therapy	% of Volume Change	% of Cases
Complete regression	invisible	55% (n=11)
Nearly complete regression	< 15 volume % of inital volume	35% (n= 7)
Partial regression	15-50 volume %	5% (n= 1)
No regression	> 50 volume %	5% (n= 1)



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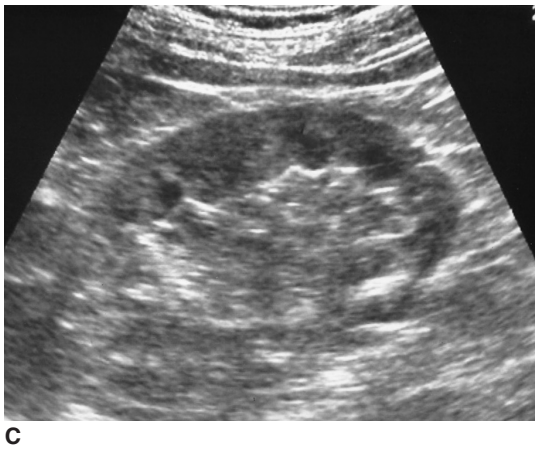

C

Fig. 2. A 76-year-old man with hematuria.
A. This patient underwent renal cyst 95% ethanol sclerotherapy 2 years previously. However, a remnant cortical cyst was noted at the lower pole of the left kidney on sonography, with a calculated volume of 35 ml.
B. Follow-up sonography 2 months later showed a significantly reduced cyst volume of 2 ml.
C. On follow-up sonography at 14 months, the cyst was undetectable, indicating a complete regression.

gamma-energy (0.08 MeV). Furthermore, holmium-166 is retained at the administration site where it forms a chelated complex with chitosan (25). The emitted beta particles ablate the lining epithelium of the cysts however, unlike in the case of external beam irradiation in which the much higher energy gamma radiation is used, only a negligible dosage attains the perilesional structures and the adjacent renal parenchyma is not damaged.

The holmium-166-chitosan complex has some positive merits as a sclerosing agent. First, sclerotherapy performed using this agent is painless. Second, the therapy can be completed in a single session with just 1−2 ml of a sclerosing agent. Third, no significant procedure-related complications have been noted. Fourth, the procedure is very simple, because there is no need to evacuate or irrigate the treatment site after the agent's instillation. Fifth, there is little risk of leakage, because the holmium-166 chitosan complex is transformed into a gelatinous substance under neutral conditions. Furthermore, this beta-ray emitting agent may allow for the effective treatment of mildly complicated cysts.

One limitation of the present study was that regular follow-up could not be performed for all patients. However, the cysts showed a tendency towards gradual obliteration and 90% of the cysts completely regressed at the final follow up. Only one cyst showed no regression. Although this patient was classified into a 'no regression' group, because of the development of the organizing hematoma, no remnants of the cystic contents remained in this case. Moreover, the mass-like hematoma had slowly involuted on the serial follow-up (43 ml initially, 38 ml immediate after treatment, and 30 ml at 30-month follow-up ultrasound). So, even if we exclude the three cases in which the follow-up period was limited to 6 months and the one case of organizing hematoma formation, the remainder of the patients showed satisfactory outcomes with complete or near-complete regression. These excellent results were probably due to the complete denudation of the epithelial lining.

In our series, 90% of the cysts had a complete or near complete regression at the final follow up after the single-session sclerotherapy using the holmium-166 chitosan complex. We believe the holmium-166 chitosan complex to be a valuable new painless sclerosing agent, which can be used for the treatment of renal cysts without significant complications.

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