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ORIGINAL PAPER

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The effect of calcium channel blockers on stone regrowth and recurrence after shock wave lithotripsy

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Abstract We evaluated the possible effects of a calcium entry blocking agent "verapamil" on new stone formation and/or regrowth of residual fragments after shock wave lithotripsy (SWL) during long-term follow-up (> 30 months) and compared the results with the success rates of adequate fluid intake. A total of 70 patients treated with SWL were randomly divided into three different groups, in the first two of which the patients received different preventive measures with respect to stone recurrence and/or regrowth. While 25 patients received a calcium channel blocking agent, verapamil hydrochloride, beginning 3 days before SWL and continued 4 weeks after the procedure, an additional 25 patients were put in an enforced fluid intake program and the remaining 20 patients received no specific medication and/or measure apart from close follow-up. Patients were followed regularly with respect to the clearance/regrowth of the residual fragments and that of new stone formation during long-term follow-up (within a mean follow-up of 30.4 months). The overall stone recurrence rate was 14% (10/70). Of the patients who became stone free (12/25, 48%) in group I, only one patient (1/12, 8.3%) showed a new stone formation during long-term follow-up. The figure was 40% (4/10) in group II patients and 55% (5/9) in group III patients receiving no specific medication. Regarding the residual stone fragments (< 5 mm) after SWL, again high fluid intake was found to be the most effective on stone regrowth rates (2/13, 15.3%). Patients treated with verapamil also had acceptable regrowth rates (3/15, 20%). Finally, verapamil treatment significantly improved the clearance of residual fragments; while 7 out of 15 patients with residual fragments passed these particles successfully, (46.5%) in this group; these figures were 46% (6/13) and 18% (2/13) in the remaining groups. Residual fragments located in lower calyces demonstrated a poor clearance rate with higher regrowth rates. Verapamil administration was found to be effective enough to limit the regrowth of residual fragments and also to facilitate residual fragment clearance after SWL. Patients receiving this medication seemed to pass the retained fragments easily in a shorter time than the others.

Keywords Shock wave lithotripsy · Stone disease · Recurrence · Calcium channel blockers

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Introduction

The objective of stone management should be complete stone clearance, prevention of stone recurrence and regrowth, preservation of renal functions, control of urinary tract infections, correction of anatomic abnormalities and of the underlying metabolic disorders. Among the available minimally invasive treatment alternatives, although shock wave lithotripsy (SWL) has revolutionized the classical treatment of most urinary calculi with its highly effective results, it is well known that a considerable number of the patients require re-treatment either due to the residual fragment and/or newly formed stones. Residual fragments may grow further especially in metabolically active patients and also constitute a possible nidus for further stone formation [1, 2].

Related with this subject, new stone formation and the fate of residual stone fragments after SWL have been subjected to several experimental as well as clinical studies [1–5]. It has been clearly shown that the stone particles located especially in the lower calyces will constitute a nidus for further stone formation and also regrow further in the absence of an effective prophylactic treatment. Additionally, residual fragments may cause recurrent urinary tract infections in the majority of the

cases. Again, stone recurrence after a successful treatment may also be encountered as a long-term problem requiring re-treatment.

Numerous treatment regimens for preventing recurrence of calcium stones have been designed and published during recent decades [6]. There is a great choice of treatment modalities, on which the clinicians have to decide based on metabolic evaluation, stone analysis data as well as the frequency of stone events. The patients can be treated conservatively by an increased fluid intake with or without dietary manipulations or by administering pharmacological agents. Among these, potassium citrate has been used as a pharmacological agent with acceptable success rates [7–11].

Calcium antagonists (a heterogeneous group which includes three main classes—phenylalkylamines, benzothiazepines, and dihydropyridines) have been found to be successful in limiting the ischemia-induced alterations in target organs, such as the heart and kidney, by maintaining blood flow. Although they differ in molecular structure, sites and modes of action, and effects on various other cardiovascular functions, they effectively lower blood pressure mainly through vasodilation and reduction of peripheral resistance. In this way, these agents can successfully increase renal blood flow to maintain normal renal physiology. Taking these specific protective effects on parenchymatous organs into account, studies dealing with the adverse effects of high energy shock waves (HESW) on renal tissue integrity have demonstrated well the protective effects of verapamil in terms of tissue alterations as well as crystal deposition in traumatized tissue [12–14].

This study was performed to obtain further insights into the effects of verapamil on stone prevention in terms of stone recurrence and regrowth of residual fragments after SWL. Long-term follow-up results (>30 months) concerning the efficacy and tolerability have been comparatively evaluated with the success rates of high fluid intake.

Materials and methods

A total of 70 patients (44 male, 26 female, M/F 1.6) from a consecutive series of renal stone patients who underwent SWL have been included in the study program. The initial study protocol was approved by the ethics committee of our faculty. Approval from the patients was obtained by written informed consent before performing any examination and/or treatment. All patients had calcium oxalate stones located in the renal pelvis without any urinary tract infection. Patients were again matched for age, stone size, and location. Overall patient age ranged from 18 to 45 years with a mean value of 33.8 years. Patient and stone characteristics are summarized in Table 1.

Following the SWL application patients were randomly divided into three different groups, in the first two of which the patients received different preventive measures with respect to stone recurrence and/or regrowth.

- Group I ($n=25$) patients received a calcium channel blocking agent Isoptin KKH film tablet (verapamil hydrochloride) 120 mg t.i.d. beginning from 3 days before SWL until 4 weeks after the procedure.
- Group II ($n=25$) patients were put in an enforced fluid intake program (to achieve a daily urinary output of more than 2.5 l) for a long-term follow-up as much as possible which was monitored closely by the study team.
- Group III ($n=20$) patients received no specific medication and/or measure apart from close follow-up.

In addition to a detailed history and urological examination, complete blood count, biochemistry parameters together with urinalysis (with urine culture sensitivity tests) were also studied. To assess the final outcome of the SWL and to evaluate the presence of residual fragments apart from a plain abdominal X-ray (including renal tomography), kidney sonography was performed at the start of the study, and at 3, 6, and 12 months after stone disintegration. Stone particles were collected by using urine filters placed onto collecting bottles and stone analysis was performed by an infrared spectroscopy method. The residual fragments are defined as all particles (<5 mm) remaining in the kidney 3 months after the last session of SWL.

No patient had previous stone disease history with stone passage, no previous intervention and metabolic abnormality could be demonstrated.

Patients were followed regularly every 3 months for the first year, every 6 months during the second year, and yearly after this period. No major complication due to SWL could be seen during early or late follow-up evaluation.

The statistical significance of the findings was evaluated by using Student's t test.

Results

The mean follow-up period was 30.4 months (24–36 months). Stone type was calcium oxalate in all patients and patients revealing other types of calculi were excluded from the study program. Mean stone size was 14.8 mm (12.6–20.8 mm). All treatments were done with a Stonelith V lithotriptor under sedo-analgesia. Maximum shock wave number in one session was 2,000 SW

Table 1 Patient and stone characteristics

Group	n	Patient age (years)	Male/female	Stone size (mm)
I	25	21–48 (32.4)	15/10 (1.5)	15.5 (13.4–22.6)
II	25	19–44 (30.6)	16/9 (1.7)	14.2 (12.0–20.0)
III	20	24–52 (34.8)	13/7 (1.8)	13.8 (10.8–21.4)
Overall	70	18–45 (33.8)	44/26 (1.6)	14.8 (12.6–20.8)

and the kV value was constant (21 kV) during all treatments.

No abnormality with respect to the pretreatment serum and urine chemistry was noted. Again none of the patients had evident metabolic abnormality including hyperoxaluria, hypercalciuria, hyperuricosuria, and hyperparathyroidism. Blood pressure and renal function were normal in all patients. Compliance with verapamil treatment and fluid intake was good in the majority of the patients. Apart from mild headache lasting 7–10 days after the initiation of the drug in four patients, no serious side effects or drug reactions have been observed during medication.

Evaluation of our data regarding the stone recurrence rate after SWL demonstrated the following results.

Regarding the results of SWL in all groups; all stones were disintegrated successfully in all groups and the success rates (during 3 months evaluation) together with stone free and residual stone rates are summarized in Table 2.

Following the treatments, the fate of residual stones and the percentage of new stone formation were closely followed under two different preventive measures in the first two groups. The overall stone recurrence rate was 14% (10/70) within a mean follow-up of months (range 24–36 months, mean 30.4). Of the patients who became stone free (12/25, 48%) in group II, only one patient (1/12, 8.3%) showed a new stone formation during long-term follow-up, whereas the figure was 40% (4/10) in group I patients and 55% (5/9) in group III patients receiving no specific medication (Table 3). There was a statistically significant difference between the second and the other two groups (I–III) ($P < 0.05$). There was no significant difference between the first and the third group ($P > 0.05$).

On the other hand again, regarding the fate of retained stone fragments after shock wave application, among the patients residual fragments (< 5 mm) 3 months after the last extracorporeal shock wave lithotripsy (ESWL) session, as revealed by renal tomography or excretory urogram, stones demonstrated either regrowth or remained stable with different percentages in all groups. Again the high fluid intake has been found to be the most effective measure from this aspect (2/13, 7.6%). Table 4 demonstrates the fate of residual stones in all groups receiving different types of measures. It was clear that in patients having stones in lower calyx, multiple stones and larger stones tended to show higher recurrence rates. With respect to both stone regrowth as well as recurrence rates, there was a statistically significant difference between the third and the other two groups (I–II) ($P < 0.05$). However, no significant difference regarding these figures could be shown between the first two groups ($P > 0.05$).

Of final importance to be noted in our study, treatment of the patients with verapamil has significantly improved the stone clearance rate in patients having residual fragments; while 7 out of 15 patients with residual fragments passed these particles successfully in group II (46.5%), these figures were 46% (6/13) and 18% (2/13) in the remaining groups.

Our results have clearly demonstrated that verapamil administration may ameliorate the outcome of these fragments by reducing the growth and agglomeration, and by increasing the clearance rate in calcium oxalate stones. With respect to the localization of residual fragments, while particles located in upper and to some extent middle calyces have been eliminated effectively in a short period of time, residual fragments located in lower parts of the kidney tended to stay within the system and grow further despite these measures.

Table 2 Evaluation of the results obtained with SWL in all groups

Group	*n*	Stone free (%)	Residual fragments (%)
I	25	10/25 (40)	15/25 (60)
II	25	12/25 (48)	13/25 (52)
III	20	9/20 (45)	11/20 (55)

Table 3 Long-term follow-up evaluation of the stone free patients after SWL

Group	Stone free	Recurrence* (%)	Stone free (%)
I	10	4/10 (40)	6/10 (60)
II	12	1/12 (8.3)	11/12 (91.7)
III	9	5/9 (55)	4/9 (45)

*P value: group I–II < 0.05, II–III < 0.05, I–III > 0.05

Discussion

Although SWL has revolutionized the classical treatment of most urinary calculi with its highly effective and safe results, it is well known that a considerable number of patients require re-treatment either due to the residual fragment and/or newly formed stones [1]. Up to 85% of the patients treated with ESWL demonstrate radiological evidence of residual stones and these residual fragments may grow further especially in metabolically active patients and also constitute a possible nidus for further stone formation. Although limited experience or data are available regarding the natural course of these fragments, it has been clearly shown that subsequent metabolic evaluation and appropriate management will certainly show lower recurrence rates when compared with the others [6].

Concerning the natural clinical course of these fragments, in their original study, during a 23-month follow-up period, Streem et al. [3] were able to show that among the 160 patients having residual fragments < 5 mm only 23.8% were stone free. Again, Candau et al. [2] were able to show that 33% of such patients were stone free at 40.6 months follow-up. During a relatively longer fol-

Table 4 Long-term follow-up evaluation of the patients with residual fragments after SWL

Group	Residual fragments (%)	Stable (%)	Regrowth* (%)	Stone free^{+} (%)
I	15	5/15 (33)	3/15 (20)	7/15 (47)
II	13	5/13 (38.4)	2/13 (15.3)	6/13 (46.1)
III	11	2/11 (18)	7/11 (64)	2/11 (18)

P* value: group I–II > 0.05, II–III < 0.05, I–III < 0.05
P^{+} value: group I–II > 0.05, II–III < 0.05, I–III < 0.05

low-up evaluation, Beck and Riehle [4] have shown that among the patients with residual fragments < 5 mm at discharge, 65% were stone free at 3 months and 41% of these patients were still stone free at 24 months. On the other hand, regarding the further growth rate of such stones, while Newman et al. [5] reported a 21.7% growth rate, Yu et al. [1] reported a 26%, and Candau et al. [2] demonstrated a 37% regrowth rate.

Several experimental as well as clinical studies evaluating the fate of residual stone fragments after ESWL have clearly shown that the stone particles located especially in the lower calyces will constitute a nidus for further stone formation and also regrow further in the absence of an effective prophylactic treatment. Additionally, residual fragments may cause recurrent urinary tract infections in the majority of the cases. Again, stone recurrence after a successful treatment may also be encountered as a long-term problem requiring re-treatment [1, 3, 4]. Taking the frequent increase in the size of residual fragments after certain types of interventions and that of new stone formation over time into account, prophylactic measures to ease the elimination of these fragments or at least limit the growth rate have gained more importance [6].

Although some options are available, some of these agents have been found to be effective and promising. These patients can be treated conservatively by an increased fluid intake with or without dietary manipulations or by administering pharmacological agents. General measures that should be undertaken are enforced fluid intake and that of dietary manipulation. An increased fluid intake gives an increased urine flow and thereby a reduction in the supersaturation level of all salts important in stone formation. In their original studies both Hoskin et al. [15] and Borghi et al. [16] were able to show the inverse association between urine volume and recurrent stone formation. In their original study, a 5-year randomized prospective study, Borghi et al. [16] found a 12% recurrence rate in those who had been encouraged to increase their fluid intake to achieve an output of 2 l/day, and a 27% recurrence rate if they were given no specific advice on urine output. There is no doubt that increased urine flow is of great value for patients with stone disease irrespective of stone composition [15, 16].

Among the pharmacological agents applied in several studies, potassium citrate demonstrated acceptable success rates with respect to stone regrowth [6–11]. In vitro studies showed that citrate inhibits calcium oxalate crystal growth on kidney stone fragments and citrate therapy has gained increasing attention in the prevention of relapses in metabolically active stone disease. Potassium citrate complexes urine calcium and is a direct inhibitor of calcium oxalate crystallization. During a 3-year follow-up Tekin [9] were able to demonstrate that the proportion of the patients remaining stone free on K-citrate was 72% while the corresponding value for untreated control patients was 20%. Again, the stone formation reduced from 1.2 to 0.1, respectively. Other agents have also been used with varying success rates in the prophylaxis of the stone disease [6].

Due to their beneficial physiological and protective effects on the parenchymatous organs such as heart, liver, and kidneys, calcium entry blocking agents have been successfully used in the management of ischemia-induced injury in these organs. Because of their renal hemodynamic effects and inhibition of calcium-mediated injury, the CAs have been found to be promising to attenuate various types of kidney damage during certain types of traumas, including radio-contrast-induced nephropathy and hypoperfusion ischemic injury that occurs during cardiac surgery [12–14]. These agents have specific effects on blood pressure control and this has been attributed largely to preferential vasodilatory action of CCBs on the afferent arterioles. As a consequence of these microcirculatory differences, CCBs reduce intraglomerular pressure to preserve GFR and renal blood flow [17, 18].

Studies again have shown that, in addition to lowering blood pressure, by acting as free radical scavengers, these agents may regulate the role of macromolecules in the mesangium; block mitochondrial overload of calcium; decrease lipid peroxidation; decrease glomerular basement membrane thickness; augment the antioxidant activities of superoxide dismutase, catalase, and glutathione peroxidase; and prevent renal cortical remodeling and scarring [17–20].

Taking the results of certain studies into account indicating that calcium channel blocker therapy may well be protective in certain models of ischemic-induced acute renal failure, while previous investigations on Madin Darby Canine Kidney (MDCK) cells demonstrated a protective effect of calcium entry blockers against shockwave-induced tubular dysfunction and also on high energy shock wave induced renal damage in both humans and animal models [21–23], results of other

studies indicated that these agents could exhibit a protective effect on shock-wave-induced tubular damage. Authors have stated that, although the underlying mechanisms are not clarified yet, direct actions on tubular cells and interference with renal hemodynamics have to be discussed [21, 22]. However, this effect may also be related to the prevention of calcium influx into injured cells or by the vasodilatory effects of verapamil that may result in an improvement in renal blood flow. Previous investigations showed that nifedipine limited calcium phosphate stone formation induced by a high-cholesterol diet in rats [24].

In a previously performed experimental study, we were able to demonstrate the protective effect of verapamil against the adverse effects of shock waves in terms of crystal deposition in traumatized tissue and new stone formation as well as tissue protection [25]. By lowering the risk of renal morphological changes after shock wave application, verapamil may be effective during long-term follow-up to limit the risk of crystal deposition and subsequent crystal formation or regrowth.

With respect to the specific protective effects of these agents in certain models of ischemic-induced acute renal failure, Jan et al. [26] claimed that this effect may be related to the prevention of calcium influx into injured cells or by the vasodilatory effects of verapamil that may result in an improvement in renal blood flow.

Apart from the protective effects of these agents on trauma-induced alterations, the effect of verapamil on urinary calcium and oxalate excretion together with its protective effect in the prevention of calcium oxalate renal stones has also been evaluated. In their original study, Iguchi et al. [27] have focused on the effect of this agent on urinary calcium and oxalate excretion and they were able to show that the calcium oxalate risk index of hypercalciuric and hyperoxaluric patients was significantly reduced after the administration of verapamil which led them to conclude that verapamil is effective in reducing urinary oxalate excretion in the hyperoxaluric patients.

Concerning the possible pathophysiological mechanisms underlying the effect of calcium antagonists on the excretion of the urine parameters, the authors stated that hypercalciuria may be the result of a reduced reabsorption of calcium in the tubulus which could possibly be due to the lower calcium influx into the tubular cells [27–29].

Last but not least, Mason et al. [14] have recently reviewed data demonstrating that at least one of the calcium antagonists, amlodipine, can regulate membrane fluidity and cholesterol deposition, stimulate NO production to recruit its biologic actions, act as an antioxidant, and regulate matrix deposition.

Depending on our own experience as well as the data reported in the literature, it is clear that these agents have evident reno-protective effects. There are two main strategies defined in recent years to have a maximum renoprotection in certain pathologies among which urinary stone disease has a specific place to care: first, pharmacologic intervention aimed at reduction of blood pressure; and secondly, dietary intervention aimed at reduction of protein intake. In addition to its specific protective effects on renal morphology and function, concerning the close association of hypertension with stone forming patients verapamil will be further effective in preserving renal integrity by lowering the blood pressure, improving renal capacity and hemodynamics.

In the light of all these observations we aimed to evaluate the possible protective effects of calcium antagonists on the regrowth, recurrence as well as clearance rate of residual fragments after SWL. Our results have clearly demonstrated that, among the treatment alternatives evaluated in our study as well as reported in the literature, high fluid intake should be the first general advice for stone formers to change the course of stone disease. Patients receiving adequate fluid intake on a regular basis will benefit from this measure to a meaningful extent.

However, we were also able to show that, in addition to carefully controlled fluid intake, verapamil therapy may be effective enough in the medical prevention of stone regrowth and residual fragment clearance after SWL. It is clear and well known that high fluid intake is the cornerstone of the therapy in stone-forming patients. Each patient should drink adequately in an attempt to lower the urine saturation and that of stone-forming risk factors. Based on our results we may claim that verapamil administration in addition to high fluid intake may be beneficial in a subset of patients (i.e. patients undergoing SWL) in order to limit the possible long-term side effects of this modality on renal function as well as morphology. High fluid intake will have a limited contribution on these possible alterations which are discussed extensively above. This treatment has also facilitated the passage of retained particles by rendering the patients stone free earlier than the untreated ones. However, it was clear that residual fragments located in lower calyces demonstrated a poor clearance rate when compared with the particles located in other parts of the kidney. Taking the traumatizing effects of HESW on renal parenchyma into account, this specific effect may be attributed to its regulatory role on the blood distribution during possible transient ischemia induced by high-energy shock waves. Again, it might be a result of its specific protective effects on high-energy shock wave induced renal tubular damage which may in turn be responsible for future crystal deposition and stone formation [30–34].

Finally, the inhibitory effect of these agents on crystal formation may again possibly be due to the lower calcium influx into the tubular cells as shown in previous experimental studies.

However, we believe that the pathophysiological mechanisms underlying the effect of verapamil on stone formation (as a result of enhanced crystal deposition) and on the excretion of the urine parameters have to be well evaluated in further experimental as well as clinical studies.

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