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How to improve lithotripsy and chemolitholysis of brushite-stones: an in vitro study

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Abstract Because of their resistance to fragmentation, treatment of brushite stones is a big problem. This study was performed to look for an improvement in therapeutic strategies by using artificial stones made of brushite (Bon(n)-stones), which are comparable to their natural counterparts. Using an ultrasound transmission technique, longitudinal wave propagation speeds were measured at different time intervals during treatment with hemiacidrin. From these and density measurements, transverse wave speed, wave impedance and dynamic mechanical properties of the artificial stones were calculated. Moreover, the microhardness of artificial stones was measured and investigations on shock wave lithotripsy (SWL) combined with initial chemolytic treatment of the stones were performed. The suggestion was confirmed that stone fragility and thus SWL can be improved by varying the physical properties of brushite stones through treatment with hemiacidrin. Additionally, we demonstrated the efficacy of Suby G in dissolving artificial brushite stones using an experimental arrangement simulating the physiological conditions in the upper urinary tract. Moreover, the efficacy of four different intracorporeal lithotripsy devices (electrohydraulic, pneumatic, laser and ultrasound) was tested and it was shown that electrohydraulic lithotripsy seems to be the best system for comminution of brushite stones.

Key words Brushite stone · Chemolysis · Hemiacidrin · Lithotripsy · Physical properties

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Introduction

Although the incidence of brushite stones (calcium hydrogen phosphate dihydrate, $CaHPO_4 \times 2H_2O$) is only about 1% [14, 15] this stone composition continues to present a serious problem in the treatment of urolithiasis. Mechanical testing of urinary calculi demonstrated that brushite stones are the hardest [5] and in vitro studies have suggested the brushite structure to be resistent to fragmentation [7, 20]. These findings are confirmed by clinical investigations of Klee et al. [17]. The authors reviewed 46 brushite calculi and reported a stone-free rate of only 11% for extracorporeal shock wave lithotripsy monotherapy. The regrowth of residual fragments was 60% in this study . These data are confirmed by Leusmann et al. [18] who observed a recurrence rate of 66.7% for brushite stones whereas a recurrence rate of 35.3% was seen with respect to all stone types.

The aim of this study was to find strategies that improve the clinical outcome of the treatment of brushite stones. Therefore an in vitro setting with artificial stones made of brushite (Bon(n)-stones) was chosen to perform standardized and reproducible investigations that look into the mechanisms of lithotripsy and chemolitholysis in detail.

Materials and methods

Materials and specimen preparation

Artificial stones (Bon(n)-stones) composed of brushite (No. 04231, Riedel de Haen) with a ball-shaped size 0.8 cm in diameter were used in this study. The production of artificial stones took place in several steps using the standard pharmaceutical operations of granulation, tableting and coating (Patent No. 19505591.8-41) [11]. Natural stones made of brushite served as a reference (21).

To prepare for the measurements of wave transmission speeds, stone samples (n = 4) were first fixed in a self-curing cold mounting resin (Koldmount, Vernon-Benshoff, Albany, N.Y.) and then cut into small slices (~2 mm thickness) with a low-speed diamond saw (Isomet, Buehler, Lake Bluff, Il.).

Wave speed measurements

In a homogeneous isotropic elastic solid, two modes of a plane wave can propagate through the medium: a longitudinal wave, characterized by the parallel movements of material particles along the wave path, and a transverse wave in which the material particles move in a direction perpendicular to the wave path. The wave transmission speeds depend on the mechanical properties of the material (bulk modulus, shear modulus, Young's modulus and Poisson's ratio). An ultrasound pulse transmission technique was used for wave speed measurements. A pair of ultrasound transducers were affixed to the opposite surfaces of each specimen, with one acting as the transmitter and the other as the receiver. Using an ultrasound pulser/receiver unit (Panametrics 5052PR, Waltham, Mass.), a high-voltage electrical pulse (220 volts into 50 ohms) was applied to the transmitter, which then sent out a short ultrasonic pulse at its resonant frequency. The ultrasonic pulse propagating through the stone specimen was detected by the receiver at the opposite surface after a transmission time Δt, monitored by a digital oscilloscope at a 300 MHz sampling rate (9314A, Le Croy, USA). The wave transmission speed was calculated as $H/\Delta t$, where H denotes the thickness of the specimen measured using a digital caliper with a precision of 0.01 mm (Ultra-Call Mark III, Fowler, Newton, Mass.).

For the measurement of longitudinal wave speed, a pair of 10-MHz transducers (Panametrics, V129-RM) was used; whereas a pair of 5-MHz shear-mode transducers (V157-RM) was used to determine the transverse wave travelling speed. To ensure good coupling between the transducers and the stone specimen, ultrasonic gel (Parker Lab, Orange, N.J.) was applied. Performing the chemolysis investigations the transverse (shear) wave travelling speed had to be calculated by assuming a constant Poisson ratio because the viscous coupler (Panametrics) needed for transverse wave speed measurements remained adherent to the surface of the specimen thus influencing the effect of the solvents.

Density measurements

Density measurements were performed using a pycnometer (Thomas Scientifics, N.J.) based on Archimedes' principle ($n = 4$). The following formula was used:

$$\rho_{S(w)} = (W_{S(w)} \times \rho_W)/(W_{S(w)} + W_W - W_{(S+W)})$$

in which, $\rho_{S(w)}$ is the stone density in wet state, $W_{S(w)}$ the weight of the stone in wet state, ρ_W the density of water, W_W the weight of the pycnometer filled with water, and $W_{(S+W)}$ denotes the weight of the pycnometer filled with stone and water.

Wave impedance, dynamic mechanical properties

With density and wave speeds determined, other physical properties of stone material such as wave impedance, bulk modulus, shear modulus, Young's modulus and Poisson's ratio could be calculated [4]. Wave impedance is an important parameter in determining the degree of wave energy reflection and transmission at the boundary between two dissimilar materials. Young's modulus is the forces per unit of cross-sectional area needed for a unit dimensional change (either elongation or shortening), whereas Poisson's ratio is the ratio between the lateral strain (e.g. shrinkage or bulging) accompanying a unit extensional or compressional strain. These properties determine the load–deformation relations of renal stone material under different types of force loading.They are intrinsic to the composition of the stone.

Effect of chemolysis on the physical properties of renal calculi

To investigate the effects on chemolysis on the physical properties of artificial stones changes of stone properties after chemolytic treatment were examined ($n = 4$). We looked into the effects of hemiacidrin (Renacidin, pH 3.85, Abbott, Chicago, Il.) on brushite stones. Synthetic urine (pH 5.7, according to [9]) served as a control ($n = 4$).

Experimentally, a calculus was bisected with one half (control group) treated with artificial urine and the other half (test group) treated with hemiacidrin. The fluids were kept in movement by a magnetic stirrer in a beaker (500 ml) at a temperature of 37°C. During treatment pH values were measured with a pH meter (type 40, Chemtrix, Hillsboro, Ohio). Measurements of the stones physical properties from the test group and the control group were performed at different time intervals to examine acute effects of chemolysis (0 min, 10 min, 1 h, 2 h).

Microhardness measurement

Hardness measures the resisting capacity of a material against penetrating loads. Crystalline plays the major role in the hardness of the renal calculi. We thus used a Vickers indenter, whose impressions were small and were within a crystalline layer, to measure the material hardness. The measurement of microhardness was performed after treatment of the specimen with hemiacidrin ($n = 8$) or artificial urine ($n = 8$) for 5 h followed by drying the specimen for 24 h. During the measurement of microhardness by a Vickers indenter a flat polished stone surface was loaded with an indenter of 100 g to produce an indentation impression in a homogeneous region on the stone surface. The Vickers indenter caused a small impression with two orthogonal, equal-length diagonals. The indentation load, when divided by the area of the impression provided the hardness of the stone material in units of pressure, an index of the stone's resistance to penetrating force. Vickers hardness was calculated as follows:

$$HV = 1.854 \times (P/\mathrm{d}^2)$$

where HV is in kg/mm^2, P (indenter load) in g and d (the averaged diagonal length of a Vickers impression) in µm.

Shock wave lithotripsy (SWL) investigations

To investigate the effects of chemolysis on SWL of artificial stones the calculi ($n = 4$) were first exposed to synthetic urine (control group) or to hemiacidrin (test group) for 60 min. Following this procedure the artificial stones were disintegrated by an electromagnetic shock wave lithotripter (Dornier Compact S, energy level 3 = 13 KV, 100 shock waves). The stones were first put in a basket located in a water basin filled with de-gassed water and coupled to the shock wave source using ultrasonic gel. The stones were automatically positioned in F2 using the Dornier basket, which was specially developed for stone comminution in vitro. Additionally, the correct position of the stones was proofed using the standard ultrasonic equipment for the Dornier lithotripter. The weight of the stones inclusive of fragments was measured before starting the investigations, immediately after chemolytic treatment and finally after SWL and drying the stones for 48 h. The weight of the fragments was assessed quantitatively by sequential sieving of the dried fragments using a series of U.S. standard sieves (mesh dimension: 4.75 mm, 2.36 mm, 1.18 mm). In this way it was possible to assess quantitatively the exact degree of comminution.

Investigations on chemolysis

Performing the investigations on chemolysis a special device has been developed to simulate the physiological conditions in the upper urinary tract. Each calculus is placed in a vessel which is held at a constant temperature of 37°C using a thermostatically controlled outer circulation. The solvents surrounding the calculus in the vessel are added at a defined speed using a liquid reservoir, tubes and pump. The weight of the calculus is measured continuously by analysis scales and documented online with a computer system.

Chemolysis of artificial brushite stones was performed using nine stones for each experiment. The dissolution speed was 80 ml/h. Suby G solution (=1, see Results), artificial urine pH 5.7 (=2), a mixture of both solutions [2 : 1 pH 3.86 (=3), 1:2 pH 4.06 (=4)] and

0.9% sodium chloride solution (=5) were used. In this experiment we exchanged hemiacidrin as this part of our investigations took place not in the United States but in Europe where hemiacidrin is not available. We decided to use Suby G solution as this solvent is very comparable to hemiacidrin (both are acid solutions, pH 3.9, with citric acid as the main and magnesium as the second most important ingredient). The artificial urine consisted of urea (25 g/l, creatinine (1.1 g/l), sodium chloride (4.6 g/l), potassium-dihydrogen-phosphate (2.8 g/l), sodium sulfate (2.3 g/l), potassium chloride (1.6 g/l), ammonium chloride (1.0 g/l) and minor quantities of calcium chloride dihydrate, magnesium chloride hexahydrate, sodium oxalate and sodium citrate.

Lithotripsy investigations

Artificial brushite stones were used to compare four different devices for intracorporeal lithotripsy (ultrasound: type 2270, Wolf; electrohydraulic: Riwolith, type 2280, Wolf; pneumatic: Calcusplit, type 276300 20, Storz; laser: MBB Litholas A, type K648101, Dornier). Two different energy levels were used for each stone composition (ultrasound lithotripsy: level 1 = 50 watts, level 2 = 125 watts; electrohydraulic lithotripsy: 5 Charr. probe, level 1 = 250 mJ, level 2 = 630 mJ; pneumatic lithotripsy: level 1 = 0.5 bar, level 2 = 2 bar, laser lithotripsy: at 5 Hz, level 1 = 100 mJ, level 2 = 140 mJ). Five stones were disintegrated at each energy level for 45 s, under direct vision. Fragments were weighed, and the percent resting weight calculated (scales MBBC100, Sartorius, USA).

Statistical measurements

Statistical measurements were performed using Mann-Whitney, Wilcoxon Rank and *t*-test.

Results

The artificial stones made of brushite were ball-shaped and identical in respect of diameter, volume and weight (Table 1). The coefficient of variation of the diameter of the stones shows that a high degree of standardization was reached. Comparing acoustic and mechanical properties of artificial brushite stones with their natural counterparts [21] it is obvious that there is a good accordance between artificial and natural stones of the same chemical composition (Tables 2, 3).

Table 1 Diameter, volume and weight of artificial stones made of brushite, mean value (±standard deviation), relative coefficient of variation (%), $n = 10$ for each group

	Diameter (cm)	Weight (g)	Volume (cm^3)
Brushite	0.8157 (±0.0298) 1.2%	0.6623 (±0.0703) 3.4%	0.2852 (±0.0311) 3.4%

Distinct differences were shown comparing the measurements of both longitudinal and transverse wave speeds, wave impedances and mechanical moduli (bulk modulus, Young's modulus and shear modulus) concerning test and control groups after treatment with hemiacidrin or artificial urine. In contrast to the control groups a marked but not significant decreasing trend in both longitudinal and transverse wave speeds was found in mechanical moduli as well as test groups (Figs. 1 and 2). There were no significant changes of density in either control groups or in test groups.

The microhardness of the hemiacidrin-treated brushite stones measured by a Vicker's indenter was significantly lower than the microhardness of the artificial urine-treated stones ($P \leq 0.05$, 72.34 ± 4.63 versus 57.83 ± 5.58 kg/mm^2).

Looking at the investigations on SWL and comparing both test and control groups it was found that the distribution of fragments after SWL is altered by initial chemolytic treatment. A clear improvement in stone comminution determined as a reduction in the relative quantity of material on the sieve with the largest fragments (4.75 mm) was found (Fig. 3).

The investigations on chemolysis showed that citric acid solutions are potent chemolytic agents for dissolving brushite calculi. The efficacy of this process is dependent on the concentration of the solvent ($P \leq 0.05$: 1 versus 2, 4 and 5; 3 and 4 versus 2 and 5; for description see above). Even artificial urine with a pH of 5.7 may lead to the dissolution of brushite stones to some extent compared with a 0.9% sodium chloride solution (Fig. 4).

Comparing the different devices for intracorporeal lithotripsy there is a relationship between the energy

Table 2 Acoustic properties of natural and artificial brushite stones, $n = 4$ for each group

Composition of stone	Density (kg m^{-3})	Longitudinal wave speed (m s^{-1})	Transverse wave speed (m s^{-1})	Longitudinal acoustic impedance (kg m^{-2} s^{-1} 10^3)	Transverse acoustic impedance (kg m^{-2} s^{-1} 10^3)
Brushite (95%) CaOx (5%)	2.157 ± 16	3.932 ± 134	1.820 ± 22	8.481 ± 354	3.926 ± 78
Brushite (artificial)	1.684 ± 36	3.789 ± 527	1.743 ± 242	6.381 ± 888	2.935 ± 408

Table 3 Mechanical properties of natural and artificial brushite stones, $n = 4$ for each group

Composition of stone	Young's modulus (GPa)	Shear modulus (GPa)	Bulk modulus (GPa)	Poisson-ratio	Vickers hardness (kg/mm^2)
Brushite (95%) CaOx (5%)	19.50	7.20	23.80	0.36	72.7
Brushite (artificial)	14.25	5.22	17.69	0.35	75.7

applied and the resting weight of artificial brushite stones. With the exception of pneumatic lithotripsy the weight of the resting fragments decreased with rising energy levels. Looking at the four different devices it was shown that electrohydraulic lithotripsy was most efficient for the disintegration of brushite stones (Fig. 5). This fragmentation system was significantly better than pneumatic lithotripsy ($P \leq 0.05$). The latter was also significantly more effective than laser lithotripsy ($P \leq 0.05$) which is more or less equivalent to ultrasound lithotripsy with regard to the disintegration of brushite stones.

Discussion

Since the introduction of extracorporeal shock wave lithotripsy (SWL), percutaneous nephrolitholapaxy (PNL) and ureteroscopic lithotripsy (URS) insufficient numbers of natural stones have been available for experimental work. In addition, the use of natural stones in experiments is problematic because of their variable morphology, chemical composition, physical properties and dissolution behaviour. Due to their lack of real stone constituents, artificial stones (e.g. plaster of paris) now available are not suitable for investigations on chemolitholysis studies. Only artificial stones made of natural materials are usable for in vitro chemolysis testing. Therefore, a stone model made of artificial brushite has been developed to serve this purpose [11, 12].

The artificial stones made of brushite are standardized (Table 1) and comparable to their natural counterparts concerning physical properties (Tables 2, 3). Investigations on SWL showed that the energy necessary for complete disintegration is correlated with the number of shock waves in the form of a hyperbolic curve, and that brushite stones are more resistant to fragmentation than stones of other chemical compositions [10]. In conclusion these artificial stones made of brushite are suitable for use in standardized and reproducible in vitro investigations and provide substance-specific information.

Measuring acoustic and mechanical properties of natural stones the results showed significant differences among various stone compositions [4]. All these stone properties are important parameters for determining the mechanical responses of renal calculi and thus stone fragility under shock wave impact. Based on these findings, it is valid to suggest that stone fragility and thus SWL treatment efficacy could be altered by varying the physical properties of the stones through chemolytic agents. Studies have shown that microhardness of calcium oxalate monohydrate and phosphate stones and their fragility can be significantly influenced by the pH values of their fluid environments [16]. Akers and his colleages [1] observed a remarkable increase in comminution for struvite/apatite stones exposed to citrate solutions.

Since the first report of chemolysis of kidney stones [6] many solvents have been introduced to dissolve stones by changing pH values. In particularly citric acid solutions such as hemiacidrin and Suby G used for struvite stones have shown their efficacy in vitro as well as in clinical trials. Thus there is a valid reason to assume that hemiacidrin may alter the physical properties of brushite stones and thus impact their treatment efficacy during SWL.

In fact, such alterations may be found regarding physical properties of brushite stones as demonstrated by wave speed measurements and wave impedances. The decreasing trends of both longitudinal and transverse wave speed and impedance show the improvement in fragmentation during SWL as a decrease of these parameters is always combined with an increase of stone comminution (Fig. 1). Bulk modulus (K), shear modulus (G) and Young's modulus (E), which determine the load–deformation relations of renal calculi under different types of stresses as well as microhardness, are also important mechanical properties. These physical properties are intrinsic to the composition of the stone and their decrease is again an indication for the impact of chemolytic agents on the efficacy of treatment during SWL (Fig. 2). Based on our shock wave investigations, the assumption for the impact of chemolytic agents on the treatment efficacy during SWL is strengthened. The distribution of fragments after SWL as measured by sieving indicates that there might be an improvement in treatment efficacy during SWL. Performing SWL after treatment of brushite stones with hemiacidrin, a

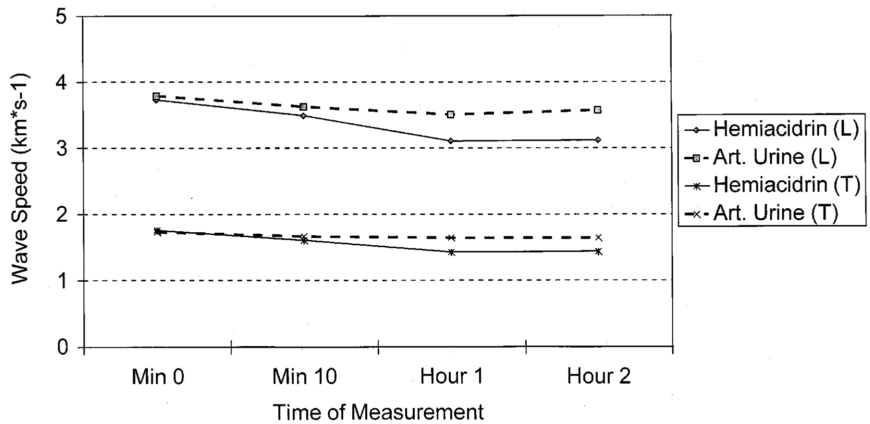


Fig. 1 Longitudinal (L) and transverse (T) wave speeds of artificial brushite stones after treatment with hemiacidrin or artificial urine; $n = 4$ for each group

reduction in the relative quantity of material remaining on the sieves with the largest mesh size was observed (Fig. 3). This result is particularly important because it is the larger fragments that are passed with the most difficulty.

However, citric acids are not only efficient by altering the physical properties of brushite stones. There are suggestions that they may also cause chemolitholysis. It was shown that the solubility of brushite is pH-dependent and increases with decreasing pH value [2]. In a clinical trial Suby G solution was able to dissolve a partial staghorn calculus made of brushite by a percutaneous approach [13]. Our investigations on chemolysis of brushite stones in vitro confirm these observations. Concentrated Suby G solution is able to dissolve brushite stones with an average speed of 16.8 mg/h (Fig. 4). This dissolution speed is reduced by dilution of the solvent with artificial urine. But even artificial urine itself with a pH of 5.7 may cause chemolitholysis to a small extent (3.4 mg/h) in comparison with 0.9% sodium chloride solution (0.7 mg/h).

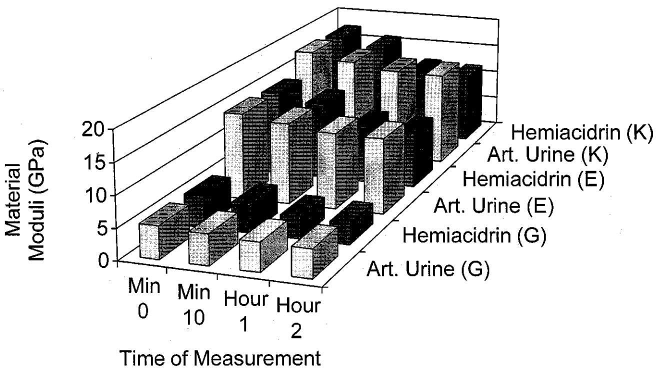


Fig. 2 Dynamic mechanical properties of artificial brushite stones after treatment with hemiacidrin or artificial urine; $n = 4$ for each group

As it was shown in in vitro as well as in clinical trials that SWL monotherapy causes insufficient fragmentation [10, 17] other lithotripsy devices have to be taken into consideration for treatment of brushite calculi. Klee et al. [17] found that treatment with PNL or URS was 92% successful in rendering the patient stone free. Therefore we examined the efficacy of four intracorporeal lithotripsy devices often used in clinical practice: electrohydraulic, laser, pneumatic and ultrasound lithotripsy (Fig. 5). It was seen that electrohydraulic lithotripsy was most effective concerning comminution of brushite stones. As described in the literature we found that fragmentation of brushite stones by pneumatic devices is also possible [8]. However, stone comminution using laser or ultrasound devices was not sufficient. This observation is confirmed by Cecchetti et al. [3] who

Fig. 3 Distribution of fragments of artificial brushite stones after treatment with hemiacidrin or artificial urine followed by shock wave lithotripsy; $n = 4$ for each group

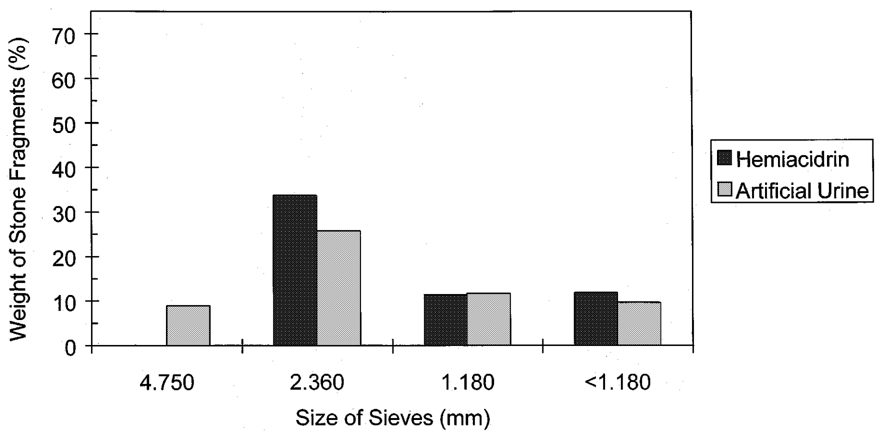
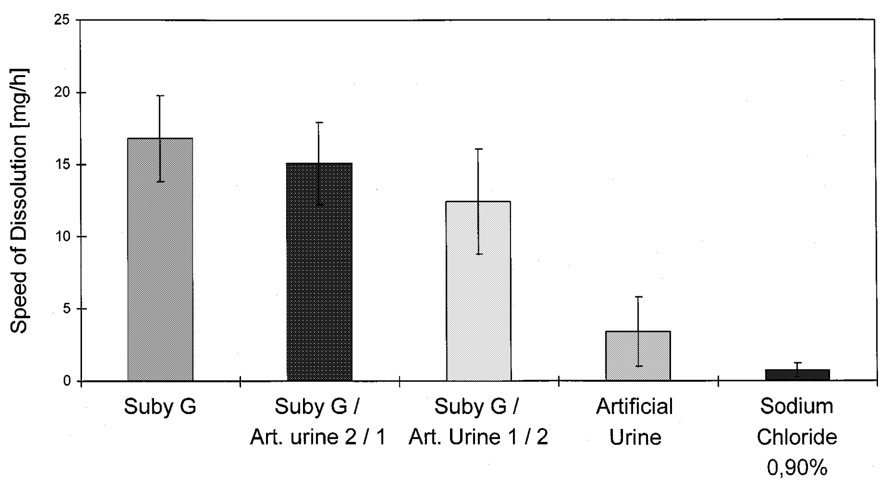


Fig. 4 Dissolution of artificial brushite stones in vitro, $n = 36$, $P \leq 0.05$: 1 versus 2, 4 and 5, 3 and 4 versus 2 and 5 (for description see Materials and methods)



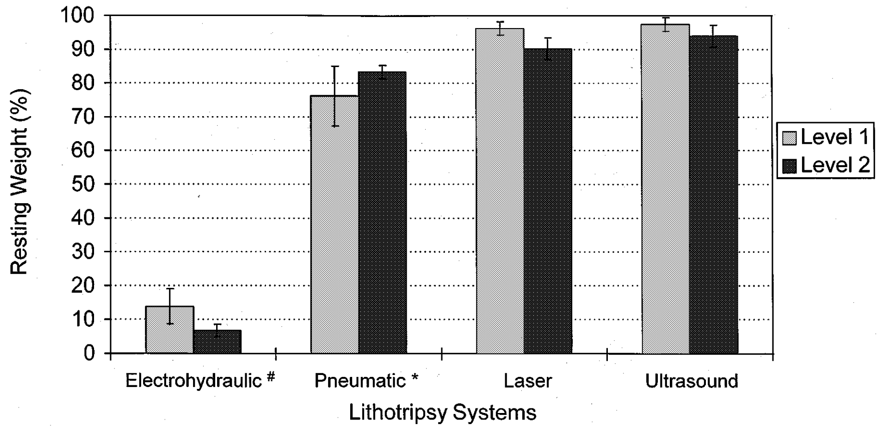


Fig. 5 Resting weight (%) of artificial brushite stones is dependent on the different lithotripsy system used; $n = 5$ for each group, # $P \leq 0.05$ for pneumatic, laser and ultrasound lithotripsy, *$P \leq 0.05$ for laser and ultrasound lithotripsy

found brushite stones to be most resistant to Nd-Yag, dye and alexandrite lasers.

In conclusion our data indicate that appropriate chemical treatment with citric acids like hemiacidrin and Suby G solution may provide a useful adjunct for improving the efficacy of stone comminution during SWL. Moreover, these agents act as chemolytic solvents so that by dissolution they have direct therapeutic effects. Schmeller and colleagues [19] demonstrated that SWL combined with chemolysis can enhance the treatment efficacy for stones by 50%. Using intracorporeal lithotripsy devices electrohydraulic systems are the first choice regarding efficacy of fragmentation.

Considering the results of our in vitro investigations and the few data in the literature the question "How To Improve The Therapy Of Brushit-Stones?" may be answered as follows:

1. In SWL of kidney stones, combination therapy with percutaneous irrigation of citric acids (Suby G solution, hemiacidrin) is recommended, especially in cases of obstruction (indication to perform a percutaneous nephrostomy).
2. In PNL of kidney stones, combination therapy with percutaneous irrigation of citric acids (Suby G solution, hemiacidrin) is recommended.
3. In ureteral stones, URS with electrohydraulic devices as first line therapy is recommended.

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