

Review

Overview of Oral Chemolysis Types and Its Effectiveness in Treating Kidney Stones

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Abstract

One of the most often diagnosed urological disorders is kidney stones with a prevalence which varies between 5% and 10% globally. In 1924, Crowell presented the first description of stone disintegration by direct irrigation. Since then, chemolysis-based dissolution therapy has been applied for the treatment of kidney stones in both primary and adjuvant settings, with different degrees of success. Depending on the type of stone, several chemolysis techniques can be applied. It has been suggested that d-penicillamine, tromethamine-E or tiopronin, and N-acetylcysteine can dissolve cystine stones. While phosphate stones are known to dissolve in acidic solutions. Renacidin and Suby G are two of the most common compounds used for chemolysis. Chemolysis can be utilized as a stand-alone therapy or as an adjuvant to shock wave lithotripsy, percutaneous nephrolithotomy, or open stone removal. The purpose of this research is to review the available information about overview of oral chemolysis types and its effectiveness in treating kidney stones. Oral chemolysis is a safe and effective treatment modality for patients with kidney stones. However, oral chemolysis is infrequently used despite the potential benefit of avoiding stone surgery with all its potential risks. The absence of trustworthy predictors of its outcome and the scarcity of high-quality data on its effectiveness are two factors contributing to its restricted utilization further clinical trial-based research is therefore needed to elaborately study the efficacy profile of oral chemolysis on various stone sizes and types.

Keywords: kidney stones, nephrolithiasis, oral chemolysis, medical treatment, Renacidin, Suby G

Introduction

Mineral build-ups that can be either free or attached with the renal papillae in the renal calyces and pelvis are termed as kidney stones. They begin to form when the urine reaches a mineral's supersaturation and contain both crystalline and organic components. The majority of stones have calcium oxalate as their principal component, and many of these stones develop on Randall's plaques, deposits of calcium phosphate found on the renal papillary surface. There is a significant prevalence of stone formation, with rates as high as 14.8% and rising, and a recurrence rate as high as 50% during the first five years of the original stone episode. The risk factors for stone development include obesity, diabetes, hypertension, and metabolic syndrome. Stones can result in hypertension, chronic kidney disease, and end-stage renal disease. Open surgical lithotomy for the treatment of symptomatic kidney stones has given way to minimally invasive endourological procedures, which have improved stone-free rates, reduced patient morbidity, and enhanced quality of life (1). Approximately 10% to 15% of people in Europe and North America suffer from urolithiasis, which is a prevalent morbidity worldwide. Stone disease is more common in hot, dry climates, with 20% to 25% of cases occurring in the Middle East. Although about 1% to 5% of all stones in developed regions are caused by paediatric urolithiasis, it is more prevalent in many developing nations (2).

Medical dissolution is without a doubt the preferred mode of care for patients with known uric acid stones. This purine metabolite's first pKa is 5.35, making it simple to alter the urinary pH for medicinal purposes. Alkaline drugs work more effectively therapeutically when urine volume is increased. Additionally, as 40% to 60% of excreted uric acid comes from exogenous sources, reducing the oral purine load from dietary sources can successfully aid in treating patients (3-5). Oral chemolysis is the main treatment for uric acid calculi except for uric acid calculi made of sodium or ammonium urate. After preliminary decompression, oral chemolysis is still a possibility even in the presence of renal backpressure. Calculus analysis, urine pH testing, and X-ray features all provide evidence that the calculus's composition is accurate. Through the alkalization of urine, chemolysis is accomplished using oral alkaline citrate or sodium bicarbonate. Although chemolysis effectiveness is strongly correlated with higher pH, the pH should be adjusted to be between 7.0 and 7.2 in order to avoid calcium phosphate calculus

development. Using ultrasound, radiolucent calculi therapy is monitored and continued (6).

Since 1924, dissolution therapy using chemolysis has been utilized in both primary and adjuvant settings to treat urinary tract stones, with different degrees of success. The type of stone can dictate the sort of chemolysis that is used. For instance, d-penicillamine, tromethamine-E or tiopronin, and N-acetylcysteine are said to dissolve cystine stones. In contrast, irrigation with sodium bicarbonate can be utilized to dissolve uric acid stones. It is also widely known that acidic solutions can dissolve phosphate stones. Renacidin and Suby G are two of the most common compounds used for chemolysis. Up until the Food and Drug Administration temporarily outlawed the use of Renacidin due to reports of six deaths that may have been connected to it in the 1960s, these citric acid solutions were both extremely popular therapies. Later, this prohibition was lifted, with a warning to avoid high pressures and infections when irrigating. But in recent years, treatment has become less common because of potential risk concerns and the development of less invasive stone surgery. Despite the Food and Drug Administration reapproval of Renacidin's use, less information about chemolysis is now accessible (7). The purpose of this research is to review the available information about overview of oral chemolysis types and its effectiveness in treating kidney stones.

Methodology

This study is based on a comprehensive literature search conducted on October 17, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about overview of oral chemolysis types and its effectiveness in treating kidney stones. There were no restrictions on date, language, participant age, or type of publication.

Discussion

Over the past few decades, there has been a significant change in how urolithiasis is treated. The novel management methods are mostly a result of the development of percutaneous nephrolithotripsy, extracorporeal shock-wave lithotripsy, and retrograde

endoscopic lithotripsy. Open renal surgery for nephrolithiasis is uncommon and only occasionally required at this time. Similarly, there are currently few indications for the use of chemolysis for stone dissolution, and its usage has been constrained by unclear cost-effectiveness. Nevertheless, chemolysis shouldn't be written off as an antiquated method because it may very well free a patient of any remaining stone particles following another stone treatment, lowering the likelihood of recurrence. The foundations of chemolysis and its potential application in the treatment of urinary calculi should therefore be understood by any urologist who manages stone disease. For a professional urologist, the fundamentals of safe and efficient chemolytic treatment are rather straightforward. However, even slight mistakes in technique might have disastrous consequences. All healthcare staff members must therefore fully know the method's specifics as well as any associated risks (8). In 1924, Crowell provided the first description of stone disintegration by direct irrigation. Urologic solution G, often known as the Suby solution, was developed in 1943 by Suby and Albright to dissolve renal calculi. Magnesium oxide, sodium carbonate, and isotonic citrate are the ingredients in solution G. Mulvaney offered renacidin as an alternative to solution G in 1957. Renacidin contains malonic and gluconic acids yet has a similar pH and buffering ability to Suby G solution (9).

Various types of oral chemolytic agents

Systemic including oral and intravenous or direct involving irrigative chemolytic dissolution are both possible. Raising urine pH by administering potassium citrate or sodium bicarbonate results in systemic chemolysis of uric acid stones. Acetazolamide, a carbonic anhydrase inhibitor, can similarly quickly alkalinize the system, albeit its usage is constrained by its propensity to generate calcium phosphate stones. Acetohydroxamic acid is frequently used to dissolve struvite stones orally. It is known to work by preventing bacteria from producing the enzyme urease, which breaks down urea to produce ammonia, which then combines with trivalent phosphates to form struvite stones. However, it has the potential to lead to hemolytic anemia. D-penicillamine or -mercaptopyronylglycine chelation is used to achieve systemic chemolysis of cystine stones. When oral chemolytic therapy for urinary tract stones does not seem to be working, direct chemolytic dissolution is chosen. This method involves irrigation of the urinary system with chemolytic fluids using nephrostomy catheters or ureteric catheters, and

the duration of irrigation can last anywhere from days to weeks. Hemicidrin, renacidin, and Tham-E are examples of frequently used chemolytic fluids. Renacidin, a multielectrolyte solution typically used to dissolve struvite stones, is primarily composed of citrate, malonate, and gluconate, which supply citrate and magnesium for chelation and dissolution of calcium and phosphate. It can be corrosive to the urothelium and has caused urosepsis-related deaths in the past, although it works well when combined with antibiotics. The most common method for removing cystine stones is Tham-E, which calls for nephrostomy catheters. In addition to extracorporeal shock-wave lithotripsy and PCNL, chemolytic dissolution therapy can also be employed to fully avoid surgery (10).

Effectiveness of oral chemolysis in light of literature

Findings of a single centre cohort study demonstrated that at three months, the total and partial response rates for stones treated with oral chemolysis were 61% and 14%, respectively, although 25% of the stones could not be removed. Stones had a median size of 9 mm and a median density of 430 Hounsfield Units. In multivariate logistic regression analysis, lower stone density ($p = 0.008$) and smaller stone size ($p = 0.025$) both significantly increased the success rate of oral chemolysis (11). Honda et al. revealed in their study that alkaline citrate was administered orally to twenty-one patients with upper urinary uric acid stones. Allopurin and hyperuricemia were coupled in this instance. Stones were eliminated in 11 out of 15 (73.3%) individuals who received only oral chemolysis. The time needed to be stone-free was shortened when alkaline citrate was administered in 4 out of 6 cases (66.7%) when paired with extracorporeal shock-wave lithotripsy. Therapy of alkaline citrate was successful in 15 out of 21 patients (71.4%) (12). A potential new method for the oral chemolysis of uric acid stones is to include theobromine in a basifying therapy that also includes citrate and/or bicarbonate. Theobromine may accelerate the breakdown of existing stones and stop the creation of new ones as results showed that the breakdown of uric acid calculi was accelerated by N-acetylcysteine, although the impact was not statistically significant. Theobromine markedly accelerated the breakdown of uric acid crystals. The combined effects of the two drugs were identical to those of theobromine. (13).

Results of a prospective study among children showed that after one session of shock wave lithotripsy, the stone-free rate was 82.1% vs. 72.9% for dissolution therapy ($p = 0.314$). During follow-up, one patient from

each group developed pyelonephritis ($p = 0.698$). Five of the 13 patients whose medical regimens failed were inconsistent with their medication intake, and three were non-compliant. Radiolucent renal stones in children can be effectively treated with medical dissolution therapy, which is well tolerated. In up to 73% of instances, shock wave lithotripsy is not necessary (2). Moran et al. demonstrated in their study that of the 11 patients, 4 reported receiving oral alkaline therapy but were later found to be noncompliant, 4 never had this therapy, and 3 just occasionally took the drug. The diaries should still be kept, and all patients were advised to self-dose to keep their urine pH between 6.0 and 6.5. Nine individuals underwent computed tomography scans, and the stone burden was confirmed in the other two patients using intravenous urography and ultrasonography. Only 3 patients (27%) needed additional treatments including ureteroscopic laser lithotripsy. Dissolution therapy is the best course of treatment for secondarily referred individuals with uric acid stones. These results imply that the ineffective follow-up or noncompliance with the original treatment regimens caused their failure. In 73% of these individuals, the stones disintegrated, necessitating no additional endourologic treatment (14).

Elsawy et al. reported in their clinical trial findings that at enrolment, the average stone surface area was 1.3 cm (range 0.16 to 11.84). At 3 months, there were 97 (53.2%), 65 (35.7%), and 20 (11.1%) patients who responded to oral dissolution treatment completely, partially, or not at all. A 6-month stone-free rate of 83% was attained with oral dissolution therapy, with 97 and 54 patients participating after 3 and 6 months of treatment, respectively. On regression analysis, the initial therapy response at 3 months ($p = 0.001$), reduced stone density at 12 weeks following treatment ($p = 0.03$), and higher urine pH at that time ($p = 0.01$) independently predicted the oral dissolution therapy response at 6 months. Oral dissolution therapy was a successful method of treating lucent renal stones, regardless of stone size. The main determinant of the probable oral dissolution therapy response after 6 months was the initial reaction to oral dissolution therapy after 3 months. Additionally, the response to oral dissolution therapy is independently influenced by treatment compliance in reaching the desired urine pH and low stone density (15). Attempts to dissolve struvite staghorn stones have been documented since 1932. A few years later, boric acid and permanganate were used to successfully treat kidney stone. Before 1943, when Suby's solution was created and then updated to Suby's solution G, chemolysis was not widely used. The latter is made up of citric acid,

magnesium oxide, and sodium carbonate. Calcium citrate and phosphoric acid are produced when citric acid breaks down into hydrogen and citrate, which bond to calcium and phosphate from the stone, respectively. Almost 60% of 118 patients treated with hemiacidrin chemolysis through a nephrostomy tube and extracorporeal shock-wave lithotripsy for struvite stones experienced complete stone clearance. Although those individuals required a lengthy hospital stay with a mean of 32 days, the rate of complications associated to therapy was notably low. Before attempting to use dissolution therapy for staghorn stones, precautions should be followed due to the possibility of infection and electrolyte disruption. Before beginning treatment it is recommended to have a minimal intrarenal pressure, and routinely measure serum phosphate and magnesium levels (16).

Salem, Sultan and Badawy reported in their study that 64.8% of participants responded overall. The pelvic or calyceal kidney stone location did not differ between responders and non-responders. The largest stone diameter was smaller in respondents compared to non-responders (P value = 0.039). In addition, respondents had a lower mean stone attenuation value than non-responders, with a P value of 0.001. On a univariate level, DJ insertions appeared to have a negligible impact on stone dissolution, but multivariate analysis indicated no difference. Radiolucent renal stones can be successfully treated with oral dissolution therapy. Stone size and density had an impact on effectiveness, with larger and denser stones having higher failure rates. Inserting a double J stent might speed up disintegration. The dissolution rate of the stones was unaffected by the baseline urine pH, hyperuricemia, or stone location (17). Although uric acid stones are the major target of dissolution therapy, there was a low level of evidence available recently. Oral chemolysis for radiolucent stones and its related predictive aspects of success were demonstrated in a number of prospective and randomized investigations. For individuals with radiolucent/uric acid stones, medical dissolution therapy is a successful treatment option for nephrolithiasis. Clinical trials are required in the future to support the optimistic findings of pilot studies evaluating a variety of medicines for cystinuria patients (18).

Conclusion

Kidney stones are treated with dissolution therapy by chemolysis in both primary and adjuvant settings, with different degrees of success. Oral chemolysis is a safe and effective therapeutic strategy for patients with

kidney stones although further clinical research can be beneficial in strengthening the efficacy of oral chemolysis.

Disclosure

Conflict of interest

There is no conflict of interest

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Ethical consideration

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

References

1. Khan SR, Pearle MS, Robertson WG, Gambaro G, Canales BK, Doizi S, et al. Kidney stones. *Nature reviews Disease primers*. 2016;2:16008.
2. Elderwy AA, Kurkar A, Hussein A, Abozeid H, Hammooda HM, Ibraheim A-F. Dissolution Therapy versus Shock Wave Lithotripsy for Radiolucent Renal Stones in Children: A Prospective Study. *The Journal of urology*. 2014;191(5, Supplement):1491-5.
3. Finlayson B, Smith A. Stability of first dissociable proton of uric acid. *Journal of Chemical and Engineering Data*. 1974;19(1):94-7.
4. Low RK, Stoller ML. Uric acid-related nephrolithiasis. *Urologic Clinics of North America*. 1997;24(1):135-48.
5. Sakhaee K, Nicar M, Hill K, Pak CY, Sakhaee K. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. *Kidney international*. 1983;24(3):348-52.
6. Abou-Elela A. Epidemiology, pathophysiology, and management of uric acid urolithiasis: A narrative review. *Journal of Advanced Research*. 2017;8(5):513-27.
7. Schillebeeckx C, Vander Eeckst K, Ost D, Van den Branden M, Deconinck S. Kidney Stone Dissolution Therapy in Phosphate Stones: A Case Report. *Journal of endourology case reports*. 2020;6(1):45-8.
8. Bernardo NO, Smith AD. CHEMOLYSIS OF URINARY CALCULI. *Urologic Clinics of North America*. 2000;27(2):355-65.
9. Gonzalez RD, Whiting BM, Canales BK. The history of kidney stone dissolution therapy: 50 years of optimism and frustration with renacidin. *Journal of endourology*. 2012;26(2):110-8.
10. Bawari S, Sah A, Tewari D. Urolithiasis: An Update on Diagnostic Modalities and Treatment Protocols. *Indian Journal of Pharmaceutical Sciences*. 2017;79:164-74.
11. Tsaturyan A, Bokova E, Bosshard P, Bonny O, Fuster DG, Roth B. Oral chemolysis is an effective, non-invasive therapy for urinary stones suspected of uric acid content. *Urolithiasis*. 2020;48(6):501-7.
12. Honda M, Yamamoto K, Momohara C, Komori K, Takada T, Fujioka H. [Oral chemolysis of uric acid stones]. *Hinyokika kyo Acta urologica Japonica*. 2003;49(6):307-10.
13. Julià F, Costa-Bauza A, Berga F, Grases F. Effect of theobromine on dissolution of uric acid kidney stones. *World journal of urology*. 2022;40(8):2105-11.
14. Moran ME, Abrahams HM, Burday DE, Greene TD. Utility of oral dissolution therapy in the management of referred patients with secondarily treated uric acid stones. *Urology*. 2002;59(2):206-10.
15. Elsayy AA, Elshal AM, El-Nahas AR, Elbaset MA, Farag H, Shokeir AA. Can We Predict the Outcome of Oral Dissolution Therapy for Radiolucent Renal Calculi? A Prospective Study. *The Journal of urology*. 2019;201(2):350-7.
16. Diri A, Diri B. Management of staghorn renal stones. *Renal failure*. 2018;40(1):357-62.
17. Salem SM, Sultan MF, Badawy A. Oral dissolution therapy for renal radiolucent stones, outcome, and factors affecting response: A prospective study. *Urology annals*. 2019;11(4):369-73.
18. Tzelves L, Mourmouris P, Skolarikos A. Outcomes of dissolution therapy and monitoring for stone disease: should we do better? *Current opinion in urology*. 2021;31(2):102-8.