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Calcium Oxalate Precipitation in Urine Following T.U.R. with Glycine as Irrigation Fluid*

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Summary. Precipitation of calcium oxalate was studied in a group of ten patients who underwent transurethral prostatectomy with glycine irrigation. Post operatively all patients showed hyperoxaluria; 60% with oxaluria higher than 10 times the critical concentration of calcium oxalate in urine. Other factors, known to favour crystallogenesis were modified during the same period: low urinary output, relative hypercalciuria and uraturia and hypomagnesuria. Thus, conditions for intraluminal precipitation of calcium oxalate were present post operatively. We suggest the use of a xanthine oxidase inhibitor to prevent hyperoxaluria.

Key words: Transurethral resection of the prostate, Glycine metabolism, Hyperoxaluria, Calcium oxalate precipitation.

Introduction

Transurethral resection of the prostate (TURP) requires continuous irrigation. Glycine used in a 1.5% solution seems more compatible with diathermy than saline and less hazardous for patients than pure water. Complications due to the 1.5% glycine solution are seldom seen because: 1) glycine is a non essential amino acid normally present in plasma; 2) enzymes can rapidly reduce high glycine levels from physiological fluids; 3) glycine gives the irrigating solution an osmolarity close to plasma. Acute water intoxication has been reported [19] and glycine or its metabolites have been implicated in visual disturbances [17], encephalopathy [18] and hyperoxaluria [6, 9]. We have shown in a recent study that hyperoxaluria was caused by a metabolic pathway common with ethylene glycol metabolism [1]. Furthermore we reported a case of acute renal failure following TURP in which hyperoxaluria was involved [2]. The mechanism of the acute renal failure is thought to be similar to the intersticial nephropathies occurring after hyperoxaluria during acute reactivation of Crohn's disease [14] or following an intestinal bypass [8] with intracytoplasmic and tubular lumen precipitation of calcium oxalates.

This study was performed to assess the degree of hyperoxaluria which normally occurs after TURP using 1.5% glycine solution and to analyse factors implicated in precipitation of crystals of calcium oxalate.

Patients and Methods

Ten consecutive patients (mean age 75.1 +/– 2 years) requiring TURP were investigated after informed consent had been obtained. Patients were maintained on a low oxalic acid diet, and were free from urinary tract infection and no urinary antiseptics had been used for five days prior to the study.

Preoperative blood samples, were collected for measurement of creatinine. A 24 h urine collection was taken for measurement of calcium, phosphorus, magnesium, creatinine, uric acid and oxalic acid excretion.

After an overnight fast, TURP was performed under general anaesthesia. During the surgery the bladder was continuously irrigated with 1.5% glycine solution (3 liter disposable bag – TRAVENOL) through an Igelsias' resector, at a constant perfusion pressure of 60 centimeters of water. An intravenous infusion of 10 to 15 $ml \cdot kg^{-1} \cdot h^{-1}$ of 5% dextrose solution was administered during the surgical procedure. After the surgery had been completed the dextrose administration was reduced to a constant rate of 1 $ml \cdot kg^{-1}$ for the next 24 h. Patients took free fluids 6 h after the procedure.

To avoid local clotting, an intravesical irrigation with heparinized normal saline was maintained for 24 h after surgery. An accurate balance of the bladder perfusion was recorded so that urine output was calculated. Blood and urinary measurements were repeated 24, 48 and 96 h after surgery.

Biochemical Measurements

Urinary oxalic acid was measured according to a colorimetric method modified from Hodgkinson [11]. The intra assay precision and recovery level were respectively 7% and 98%. This improved technique rendered the assay independant from glycine and glycolate concen-

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Table 1. Creatinine clearance and urinary excretion of organic acid, ions and creatinine measured pre-operatively and the first, second and fourth day after surgery. Stat. denotes F value from a one way variance analysis

	Oxaluria μmol/24 h	Uraturia μmol/24 h	Calciuria mmol/24 h	Phosphaturia mmol/24 h	Magnesuria mmol/24 h	Creatiniuria μmol/24 h	Creatinine Clearance $ml \cdot min^{-1}$
Normal value	< 400	<4,200	<8.5	<29	1 to 12	8,800	>1
Pre-operative	304 ± 29	3,881 ± 274	4.2 ± 0.6	21.9 ± 2.1	3.04 ± 0.41	9,340 ± 487	1.36 ± 0.09
Day 1	5,560 ± 1,116	4,550 ± 465	4.7 ± 0.6	27.8 ± 4.3	1.96 ± 0.25	7,826 ± 468	1.14 ± 0.07
Day 2	1,311 ± 115	4,765 ± 475	5.7 ± 0.9	23.7 ± 2.2	4.21 ± 0.67	10,680 ± 780	1.4 ± 0.11
Day 4	530 ± 68	3,860 ± 400	4.1 ± 0.7	21.6 ± 2.25	3.03 ± 0.38	9,195 ± 875	1.26 ± 0.12
Stat.	$F = 19.4$ $p < 0.001$	NS	NS	NS	$F = 6.1$ $p < 0.01$	$F = 6.4$ $p < 0.01$	NS

Table 2. Urinary concentration of organic acid, ions, creatinine and tubular reabsorption rate of phosphorus measured pre-operatively and at day one, two and four after TURP

	Oxaluria $\mu mol \cdot l^{-1}$	Uraturia $\mu mol \cdot l^{-1}$	Calciuria $mmol \cdot l^{-1}$	Phosphaturia $mmol \cdot l^{-1}$	Phosphorus Tubular Reabsorption	Magnesuria $mmol \cdot l^{-1}$
Prea-operative	195 ± 20	2,845 ± 473	2.86 ± 0.54	15.78 ± 2.97	82.9 ± 1.5	1.99 ± 0.27
Day 1	3,971 ± 682	3,612 ± 771	3.36 ± 0.41	20.64 ± 2.93	72.3 ± 4.4	1.52 ± 0.31
Day 2	859 ± 121	2,953 ± 393	3.74 ± 0.72	15.03 ± 2.32	80.3 ± 2.5	2.57 ± 0.46
Day 4	270 ± 34	2,181 ± 359	2.17 ± 0.41	12.21 ± 2.21	83.6 ± 1.4	1.64 ± 0.26
Stat.	$F = 27.9$ $p < 0.001$	NS	NS	NS	$F = 4.5$ $p < 0.025$	NS

trations in urine. Uric acid was analyzed by the method of Henry, Sobel and Kim [10]. Calcium and magnesium were estimated by flame photometry and phosphorus by the method of Dryer [7]. Creatinine was assessed by the Jaffe technique using a Beckman analyser.

Normal values for the laboratory and the range of age concerned are displayed in each table.

Parameters of Crystallogenesis

From the 24 h urine collection the following ratios were calculated: calcium/creatinine, magnesium/calcium and uric acid/creatinine.

Relative supersaturation and activity product were calculated following the usual procedure [15] and a nomogram for calcium oxalate was built taking in account the very high oxalate concentration. This nomogram is based on standard logarithmic procedures for calculating the saturation of urine with calcium and oxalic acid concentrations. Calcium and oxalic acid concentrations are taken together, the saturation value is read directly at the intersection with the saturation axis. The right scale on the saturation axis is expressed in absolute value (activity product-AP). The left scale is expressed as the relative supersaturation (RS) taking into account the theramodynamic formation and solubility products of calcium oxalate. On this scale a value under 0 indicates that the urine is under saturated with calcium and oxalic acid and should redissolve any preexisting crystals of calcium oxalate. A value between 0 and 1 indicates that the urine is in a metastable region of supersaturation, the growth and aggregation of preexisting crystals may occur but not the spontaenous formation of new crystals. A value greater than 1 indicates that spontaenous precipitation of calcium oxalate is likely to occur.

Statistical Analysis

Results are given as mean +/− SEM. Differences between successive values were analyzed by a one way variance analysis programme.

Results

Renal Function

Data are exposed in Tables 1–3. The evolution of diuresis showed an early decrease of urinary output post operatively (−16%), associated with a fall in the creatinine clearance (−16%). Creatininuria exhibited a significant diphasic evolution with an early decrease (−16%) at 24 h post surgery followed by an increase (+14% from control) at 48 h.

Organic Acid Metabolism

A 15 fold rise in oxaluria occurred after the surgery. The fourth day post surgery oxaluria per 24 h was still higher than normal. Oxalic acid concentrations in urine followed the same variations but returned to normal on the last measurement. All these variations were significant. Urinary excretion of uric acid increased slightly, but not significantly, during the first 24 h and reached the preoperative value

Table 3. Evolution of diuresis and urinary ratios before and during the four days following TURP

	Diuresis ml/24 h	Urate/Creatinine Urinary ratio	Magnesium/Calcium Urinary ratio	Calcium/Creatinine Urinary ratio
Pre-operative	1,700 ± 300	0.42 ± 0.03	0.83 ± 0.08	0.46 ± 0.07
Day 1	1,440 ± 138	0.60 ± 0.07	0.44 ± 0.06	0.60 ± 0.09
Day 2	1,800 ± 220	0.45 ± 0.04	0.88 ± 0.17	0.53 ± 0.07
Day 4	2,045 ± 200	0.42 ± 0.03	0.97 ± 0.2	0.44 ± 0.07
Stat.	NS	$F = 6.6, p < 0.01$	$F = 3.2, p < 0.05$	NS
Normal value		< 0.30	0.8 to 1	< 0.56

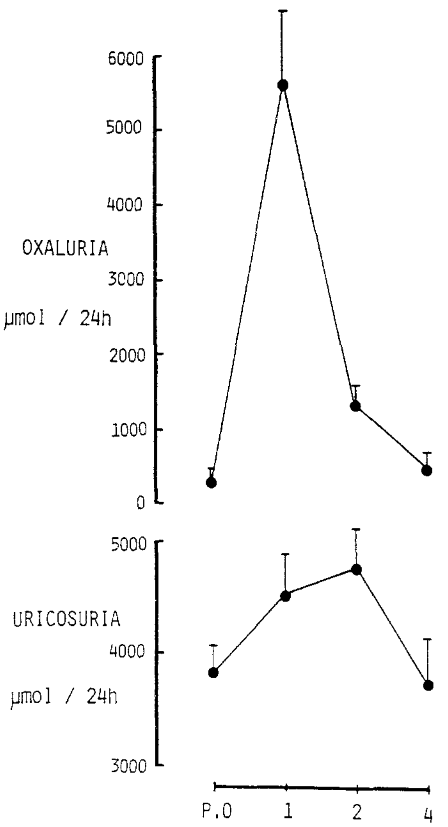

Fig. 1. Variations of 24 h urinary excretion of oxalate ($p < 0.001$) and uric acid (N.S.) after TURP utilizing 1.5% glycine solution

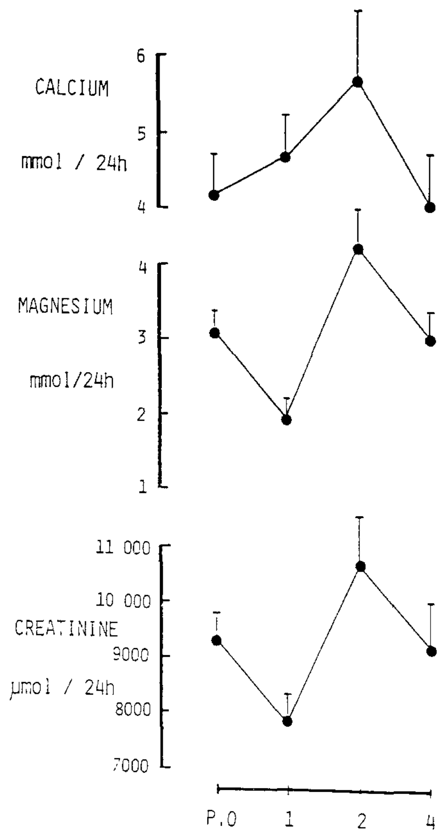

Fig. 2. Variations of 24 h urinary excretion of calcium (N.S.), magnesium ($p < 0.01$) and creatinine ($p < 0.01$). *P.O* denotes preopra-tive data; *1, 2* and *4* denote values at day one, day two and day four after TURP utilizing 1.5% glycine solution

at 96 h. However, uric acid excretion related to creatininuria was significantly higher during this period (Fig. 1).

Metabolism of Ions

Calciuria was increased by 11 and 34% at 24 and 48 h post surgery, while phosphaturia was enhanced only during the first 24 h correlating with a decrease in the tubular reabsorption rate. These variations were not statistically significant, except for the tubular reabsorption rate. Magnesuria fell significantly the first day after TURP and returned to normal at day two, following an evolution parallel to creatininuria (Fig. 2).

Parameters of Crystallogenesis

Urinary excretion of calcium in relation of cratinine did not increase significantly, the slight rise in calciuria occurring at a time when creatininuria was also enhanced. Urinary excretion of magnesium related to calcium decreased significant-

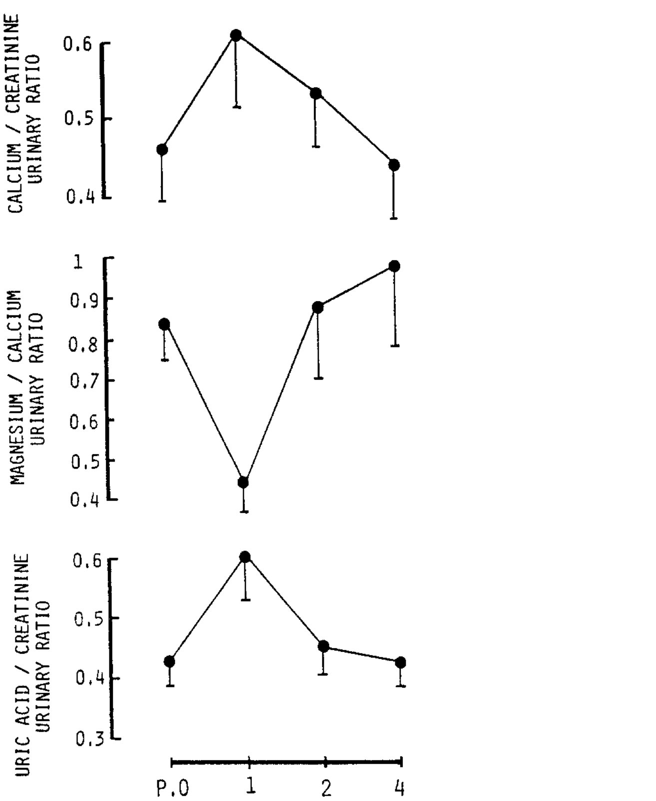

Fig. 3. Variations of three urinary ratios: uric acid/creatinine ($p < 0.01$), magnesium/calcium ($p < 0.05$), calcium/creatinine (N.S.). Modifications occur at day one post TURP at a time when hyperoxaluria is maximal favouring crystal formation in urine

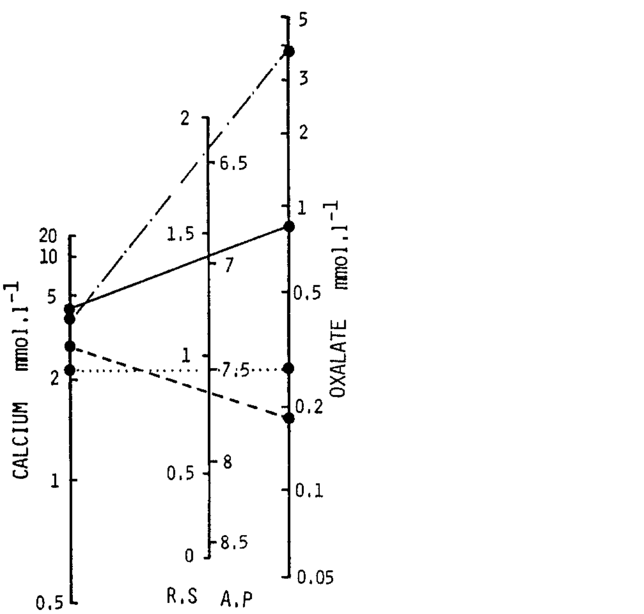

Fig. 4. Nomogram for calcium oxalate saturation levels has been built for very high oxalate concentrations. On the *right* scale oxalate urinary concentration, on the *left* calcium urinary concentration. The *central* scale shows on the left the relative supersaturation (*R.S.*) and on the right activity product (*A.P*) (see text for explanations). 0 — — — 0 denotes preoperative value, 0 — • — • —) denotes data at day one after TURP, 0———0 denotes data at day two, 0 • • • • • 0 denotes data at day four

ly within the first day post surgery and returned to normal at day 2 (Fig. 3). Preoperatively, patients were within the metastable region. The combination of the relative hypercalciuria and the large increase in oxaluria on day one projected the product value over the spontaneous precipitation part of the scale. At 48 h, patients remained within the precipitation zone despite the reduction in oxalic acid concentration. On the fourth day after surgery the decrease in oxalic acid concentration resulted in a fall to below 1 on the relative supersaturation scale (Fig. 4).

Discussion

During the first 24 h after TURP using 1.5% glycine solution irrigation, a number of factors combine to favour crystals formation: low urinary output, increased oxaluria, enhanced calciuria and uraturia and a decreased urinary level of magnesium.

The low urinary output was not prominent and was accompanied by a minor and insignificant decrease in the creatinine clearance. The increase in creatinine excretion occurring at day 2 might be due, either to the release of creatinine stored during the first 24 h, or to a rise in creatinine production: glycine metabolism increases the creatinine level [1] as well as the muscular catabolism induced by a relative confinement of patients to bed.

The high level of oxaluria following TURP using glycine solution has been described by Crawhall [6] as early as 1959. In our study, however, the rise in oxalic acid excretion was larger and more common than that reported by Fitzpatrick [9], differences which may be explained by case selection since they measured oxalates only when patients were found to be hyponatremic after TURP. Leon [13] has shown that hyponatremia is inadequate as a measure of glycine resorption. These asymptomatic resorptions of glycine have been seen in 45% of patients and no correlation could be found between the amount of the resorbed solution and haemodilution in our previous study [1].

Berland [3] has demonstrated that an urinary concentration up to 300 $\mu mol \cdot l^{-1}$, whatever the calcium concentration, induces a critical level of supersaturation. This critical concentration was greatly exceeded on the first and the second day after surgery in 60% of our patients, who had more than 10 times this level on day 1 and 50% had still 3 times this concentration on day 2. All but two patients had, however, returned to below the critical level by the fourth post operative day because of an increased urine output, while oxalic acid excretion remained higher than normal at this stage.

The slightly enhanced calciuria, attributed to immobility post surgery, contributed to a supersaturation of urine and to an increased precipitation of calcium oxalate as evidenced by the nomogram.

Hyperuraturia has also been demonstrated to be relevant to crystallogenesis in patients with calcium oxalate lithiasis [5]. 80% of urate levels recorded in this study were higher than the normal level (4,200 mmol/24 h in normal subjects). Hypomagnesuria is another well documented crystallogenetic factor. It has been demonstrated that a magnesium depletion causes calcification in the proximal tubule in the rat [4] and Johanson [12] has shown, in a comparative study, that patients with an history of urolithiasis presented a magnesium to calcium ratio significantly lower than normal subjects. In this study, magnesiuria was lower on day 1 associated with a significant decrease of the magnesium/ calcium ratio. These factors constituted an extra crystallogenic risk.

Thus, the first and the second days after TURP were characterized by the conjunction of several crystallogenetic factors. It must be pointed out that the use of glycine solution was restricted to the operative period (44 min +/– 7 min TURP duration, 8.1 litres +/– 2 litres glycine solution infusion), a saline irrigation replacing the glycine solution during the postoperative course. The same fluid as during surgery can also be used for irrigation increasing the amount of resorbed glycine. Fitzpatrick [9] has shown that the duration of hyperoxaluria was longer than two weeks post TURP if these conditions are used.

This study was motivated by the observation of acute renal failure following TURP, induced by hyperoxaluria after a prolonged and haemorragic resection. This acute renal failure had several similarities with those occurring with Crohn's disease or intenstinal bypass [8, 14]. Pathological findings strongly implicated oxalate crystaluria in the pathogenesis of the renal injury, with intracytoplasmic and tubular lumen deposition of crystals and giant cell transformation, both in the proximal and distal convoluted tubules. In this study, we tried to estimate crystallogenesis by analysis of terminal urine, and to compare the result to that obtained in other similar situations. The mean rate of oxaluric excretion was more than 5 times higher in our results than those published by Nordenvall after intestinal bypass, and in some patients the urinary excretion was higher than 12,500 μmol/24 h. It may be possible that these higher levels induce luminal precipitation. It may be possible to minimise this hyperoxaluria by perioperative use of an inhibitor of xanthine oxidase which is the enzyme involved in the metabolism of glycine to oxalic acid [1].

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