5 Years Follow-up of Tak Protocol in Stone Recurrence/Regrowth after Kidney Stones Removal

Ekkapong Konkaew[1]*, Mutita Subcharoenwai[1] and Kittisak Olankitcharoen[2]

[1]Somdejphrajaotaksinmaharaj Hospital Medical Education Center, Tak, 63000, Thailand

[2]Department of Surgery, [1]Somdejphrajaotaksinmaharaj Hospital, Tak, 63000, Thailand

* Corresponding author. E-mail address: Research.taksin@hotmail.com

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Abstract

Kidney stone is a risk factor for chronic kidney disease. Nephrocalcinosis or renal crystal deposition can lead to progressive loss of GFR that increase rate of complication and hospitalization. This research aims to evaluate 5-years follow-up of Tak Protocol in stone recurrence/regrowth, complication, hospitalization and reintervention after stone removal, compare with patients who loss follow-up. A retrospective cohort study of 106 patients with renal stone who after stone removal intervention were enrolled. All patients were divided in two groups. The protocol group (N = 70) was defined in patients who following up consistently through 5 years, and the loss follow-up group (N=36) serving as controls. Plain films KUB were used to detect stone recurrence and regrowth through 5-years follow-up. Complication, hospitalization and reintervention were reviewed from electronic medical recording database. 106 patients complete 5-years follow-up observation period. The average ages were 53.6 and 48.4 years for the protocol and loss follow-up groups, respectively. Most of 28 patients (40.0%) of protocol and 16 patients (44.4%) of loss follow-up were hypertension, whereas 25 patients (35.7%) and 15 patient (41.7%) were no underlying disease. In the stone free group, 90.5% of protocol group and 9.5% of loss follow-up group were still stone free at 60 months. In comparison with loss follow-up, stone free rate was 8.88(95%CI; 2.33-33.88, p<0.001) in protocol group. As a results of the residual stone group, protocol were 7.33(95% CI; 1.06-50.60, p= 0.006) in stone free rate. Stone recurrence/size increased was found in 9.5% and 84.6% of protocol and loss follow-up group, while the result of stone size unchanged/decreased was no significant different in statistic. The recurrence and regrowth rates at one, two, three, four and five years were 2.39, 1.23, 0.84, 0.98 and 0.54 per 1,000 patient-months in the protocol group and were 7.11, 14.84, 6.57, 1.22 and 6.61 per 1,000 patient-months in the loss follow-up group, the IRR was 2.97 in the first year after intervention. The stone recurrence and regrowth were found in five years follow-up. Loss follow-up group was a higher rate than Tak protocol group. In conclusion, patient who has history of stone removal should be encouraged for lifestyle modification and made the appointment for following up at least 5 years. This protocol was shown the benefit in reducing complication and hospitalization rate.

Keywords: 5 Years follow-up, Tak protocol, Stone recurrence, Kidney stones removal

Introduction

Currently, there are several kidney stone removal therapies that provide better results and acceptable rate of complication after stone removal. Especially, Extracorporeal Shock Wave Lithotripsy (ESWL) and Percutaneous Nephrolithotomy (PCNL) are widely used for kidney stone management. Unfortunately, they did not change the underlying of metabolic abnormality. Most common stone was calcium oxalate (80.86%) (Tosukhowong et al., 2007) which hypocitraturia is an important risk factor for calcium stone. Stone recurrence is usually occurred after post-operative management even in patient with stone free status. The residual stone created the new nucleation of stone that would be caused of the recurrence. In Thailand, most of the first episode recurrence stone formation was occurred in two years (27-50%) (Lojanapiwat et al., 2011).

At Somdejphrajaotaksinmaharaj Hospital (TSM) data in 2015-2017, about 30% of out-patient department (OPD) patients who visit in urology clinic presented with kidney stone problems such a new stone formation, recurrent stone or increased in serum creatinine. The recurrence rate was about 20%. At present, it was not clearly recommendation for routine following up and treatment suggestion after intervention, in setting which stone analysis was not evaluated. "Tak protocol" was created for routine following up and long-term management. These patients were checked up their urine profile, medication compliance and life style modification-adjustment. This protocol aimed to prevent the stone recurrence and reduce the complication. Lifestyle modification and potassium citrate adjustment were encouraged by urologist. None of the long term-study has been reported the rate of stone recurrence / regrowth in setting which unknown stone analysis. Therefore, this study was evaluated 5-years follow-up of Tak Protocol in stone recurrence/ regrowth, complication, hospitalization and reintervention after stone removal, compare with patients who loss follow-up. In order to gets the accurate data for planning stone management in long-term, leading to the economic implication.

Methods and Materials

A retrospective cohort study was performed in patient treated by ESWL or open surgeries who were admitted at urological department, TSM Hospital between January 2009 and December 2012. Medical records were reviewed through five years after intervention. Eligible patients were diagnosed with Hydronephrosis with renal and ureteral calculous obstruction (N132), Calculus of kidney (N 200), Calculus of ureter (N 201), Urinary calculus, unspecified (N 209). The patients were treated by Nephrotomy, Nephrolithotomy (55.01), Pyelotomy, Exploration of renal pelvis, Pyelolithotomy (55.11), Ureterotomy (56.2) and Extracorporeal Shock Wave Lithotripsy (98.51). Research sample size was calculated by yamane's formla. Included patients were completed data of the follow-up plain film kidney urinary bladder (KUB) at least once a year. Patients who revisited and completed data (plain film KUB and clinical data) were considered in the loss follow-up group. Plain films KUB were used to indicate stone recurrence and regrowth through 5-years follow-up. All films were reviewed by the same urologist. The reappearance of stones on plain film KUB after a certain stones free result was considered as stones recurrence. Stone regrowth was defined by increasing in diameter of the residual stone size, comparing to last plain film KUB. Complication, hospitalization and re-intervention were reviewed from electronic medical recording database.

One hundred and eighty-two patients were assessed for eligibility. In this study excluded seventy six patients who incomplete the data (no revisiting of clinical data and plain film KUB). One hundred and six patients were included for the present study. (Figure 1)

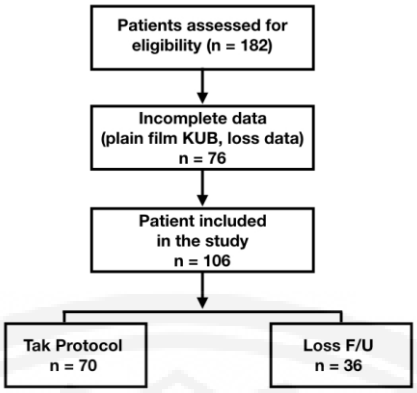

Figure 1 Flow chart of patients included in the study

In eligible patients were divided in two groups. Tak protocol group was defined in patients who following up consistently through 5-years. The other patients with complete revisit data were recruited into the loss follow-up group. Loss follow-up group was a patient who had no data or visited less than 2 time in 5 years.

Tak protocol was a guideline for management patients after stone removal intervention. This protocol was implicated to all patients at urological unit, TSM Hospital. Lifestyle modifications in dietary and fluid intake were encouraged by urologist in every visiting. Urine pH was done in every visit for screening hydration status. Potassium citrate was used in all patients for urine alkalization with dosage 60 mEq/day. If urine pH was more than 6.5-7, potassium citrate would be reduced to half-dose. Discontinuation of potassium citrate were considered in patient who had urine pH lower than 5 and adequate fluid intake and urine specific gravity lower than 1.010 at 3 times consecutively. All patients were followed up every month in the first 2 years and then every 3-4 months, depend on patient compliance.

The statistical analyses were carried out by using SPSS statistics software. Chi-square and Fisher's exact tests were used to compare stone recurrence/regrowth, complication, hospitalization and reintervention between protocol and loss follow-up group. Incidence rate per 1000 patient-month and incidence rate ratio were described. A p-value of less than 0.05 was considered as statistical significance.

The protocol and documents need for this study have been reviewed and approved by the Ethics Committees of TSM Hospital.

Results

Of 182 patients included, 106 patients complete 5-years follow-up observation period. Seventy patients were protocol group. The average ages were 53.6 ± 13.1 and 48.4 ± 11.7 years for the protocol and loss follow-up groups, respectively (Table 1). Gender was not different in each group. Most patients had normal BMI (61.4% and 63.9%). The occupational of protocol group consisted of agriculture 24 patients (34.3%) and 14 patients (38.9%). The second most common was employee and building contractor. The underlying diseases were found. Most of 28 patients (40.0%) of protocol and 16 patients (44.4%) of loss follow-up were hypertension. 25 patients (35.7%) and 15 patient (41.7%) were no underlying disease. The single stone more occurred in protocol (51.4% versus 48.6%), contritely to the loss follow-up group. The stone located most frequently in renal pelvis in protocol group (31.4%) and lower calyx in loss follow-up group

(50.0%). The median of urine pH and urine specific gravity was 6.0/1.015 in protocol group, same as a result of loss follow-up group. Most of intervention of two groups was ESWL (81.4% and 86.1%). The change of the stone, assessed at 60 months follow-up, is shown in Table 2.

Table 1 Baseline characteristics of patients. Values are numbers (%) unless stated otherwise

Information	Protocol; n = 70	Loss F/U; n = 36
Age (years) ; Mean ± SD	53.6 ± 13.1	48.4 ± 11.7
Gender (M:F) ; Number	37:33	21:25
BMI		
- <18.5 kg/m^2	6(8.6)	1(2.8)
- 18.5-24.99 kg/m^2	43(61.4)	23(63.9)
- ≥ 25 kg/m^2	21(30.0)	12(33.3)
Occupation		
- Agriculture	24(34.3)	14(38.9)
- Employee/ Building contractor	21(31.0)	12(30.6)
- Government officer	1(1.4)	-
- Merchandise	8(11.4)	5(13.9)
- Others	16(22.9)	6(16.7)
District		
- Mueang Tak	23(32.9)	7(19.4)
- Ban Tak	21(30.0)	5(13.9)
- Sam Ngao	7(10.0)	6(16.7)
- Wang Chao	11(15.7)	2(5.6)
- Mae Ramat	1(1.4)	4(11.1)
- Mae Sot	4(5.7)	8(22.2)
- Tha Song Yang	3(4.3)	1(2.8)
- Phop Phra	-	-
- Umphang	-	3(8.3)
Underlying disease		
- Hypertension	28(40.0)	16(44.4)
- Diabetes Mellitus	4(5.7)	2(5.6)
- Dyslipidemia	12(17.1)	6(16.7)
- Cardiovascular disease	1(1.4)	1(2.8)
- Chronic kidney disease	7(10.0)	5(13.9)
- Others	13(18.6)	4(11.1)
- No underlying	25(35.7)	15(41.7)
Stone number		
- Single	36(51.4)	15(41.7)
- Multiple	34(48.6)	21(58.3)
Stone location		
- Renal pelvis	22(31.4)	6(16.7)
- Lower Calyx	11(15.7)	18(50.0)
- Middle Calyx	5(7.1)	-
- Upper Calyx	8(11.4)	3(8.3)
- Staghorn	18(25.7)	4(11.1)
- Ureter	6(8.6)	5(13.9)

Table 1 (Cont.)

Information	Protocol; n = 70	Loss F/U; n = 36
Urinalysis		
- Urine pH ; Median(min-max)	6.0(5.0-7.5)	6.0(5.0-7.0)
- Urine Specific gravity ; Median	1.015	1.015
Intervention		
- Nephrotomy, Nephrolithotomy	9(12.9)	4(11.1)
- Pyelotomy, Exploration of renal pelvis, Pyelolithotomy	1(1.4)	-
- Ureterotomy	-	1(2.8)
- Extracorporeal Shock Wave Lithotripsy	57(81.4)	31(86.1)
- Combined	3(4.3)	-

Table 2 Stone-forming activity at 60 months (Overall n = 106)

Stone-forming activity	Stone Free (%) n = 34				Residual Stone (%) n = 72			
	Protocol n = 21	Loss F/U n = 13	RR (95% CI)	P-value	Protocol n = 49	Loss F/U n = 23	RR (95% CI)	P-value
Stone free	19(90.5)	2(9.5)	8.88 (2.33-33.88)	<0.001*	17(34.7)	1(4.3)	7.33 (1.06-50.60)	0.006
Stone size unchanged	-	-	-	-	15(30.6)	4(17.4)	1.73 (0.66-4.36)	0.235
Stone size decrease	-	-	-	-	8(16.3)	2(8.7)	1.69 (0.47-6.14)	0.485
Stone recurrence/ size increased	2(9.5)	11(84.6)	0.11 (0.03-0.43)	<0.001*	9(18.4)	16(69.6)	0.23 (0.11-0.49)	<0.001

* Fisher's Exact Test

In the stone free group, 90.5% of protocol group and 9.5% of loss follow-up group were still stone free at 60 months. In comparison with loss follow-up, stone free rate was 8.88 (95%CI; 2.33-33.88, p<0.001) in protocol group. Similarly to the residual stone group, protocol were 7.33 (95%CI; 1.06-50.60, p=0.006) in stone free rate. Stone recurrence/size increased was found in 9.5% and 84.6% of protocol and loss follow-up group respectively, which were statistically different. At the same 60 months follow-up, in the group with the residual stone, 18.4% and 69.6% of patients were found stone recurrence/size increased in the protocol and loss follow-up group, respectively (RR=0.23, 95%CI; 0.23 (0.11-0.49), p<0.001). Whereas the results of stone size unchanged/decreased was no significant different in statistic. The recurrence and regrowth rates at one, two, three, four and five years were 2.39, 1.23, 0.84, 0.98 and 0.54 per 1,000 patient-months in the protocol group and were 7.11, 14.84, 6.57, 1.22 and 6.61 per 1,000 patient-months in the loss follow-up group, the IRR was 2.97 in the first year after intervention. IRR of the second year was 12.06, whereas the results of the third and fourth years was decreased (IRR=7.82, and IRR=1.24, respectively). The fifth year, IRR was 12.24. (Table 3)

Table 3 Incidence rate and incidence rate ratio of stone recurrence/ regrowth at 1 to 5 years

Year/Group		Recurrence/Regrowth (case)	Follow-up time (month)	Incidence rate per 1,000 patient-month	IRR
1st year					Ref. 2.97
	Protocol	2	836	2.39	
	Loss follow up	3	422	7.11	
2nd year					Ref. 12.06
	Protocol	2	1,626	1.23	
	Loss follow up	11	741	14.84	
3rd year					Ref. 7.82
	Protocol	2	2,367	0.84	
	Loss follow up	5	760	6.57	
4th year					Ref. 1.24
	Protocol	3	3,054	0.98	
	Loss follow up	1	816	1.22	
5th year					Ref. 12.24
	Protocol	2	3,653	0.54	
	Loss follow up	7	1,058	6.61	

The complication of stone at 60 months follow-up is shown in Table 4. In stone free group, 17.6% of loss follow-up group had a complication. The risk ratio was 0.058 in protocol group (95%CI; 0.006-0.573, p=0.007). Similarly to the residual stone group, the RR was 0.128 (95%CI; 0.039-0.417, p=0.001) in the complication. Urinary tract obstruction with hydronephrosis was found two cases in stone free group and 11 cases in residual stone group. Three cases developed renal failure in stone free group. Hospitalization due to complication in the protocol group were 0.276 (95%CI; 0.153-0.497, p=0.005) and 0.750 (95%CI; 0.008-0.687, p= 0.011). The results of reintervention was significant different between protocol and loss follow-up group, whether stone free or residual stone.

Table 4 Complication, Hospitalization, Reintervention and Duration of potassium citrate use at 60 months

Stone-forming activity	Stone Free (%) n = 34				Residual Stone (%) n = 72			
	Protocol	Loss F/U	RR (95% CI)	P-value	Protocol	Loss F/U	RR (95% CI)	P-value
Complication;N(%)	1(2.9)	6(17.6)			6(8.3)	12(16.6)		
- UTO	1	2	0.058		6	11	0.128	
- UTI	-	1	(0.006-0.57)	0.007*	-	1	(0.039-0.41)	0.001
- Renal failure	-	3			-	-		
- Hypertension	-	-			-	-		
Hospitalization due to complication	-	5(14.7)	0.276 (0.15-0.49)	0.005*	1(1.4)	5(6.94)	0.75 (0.008-0.68)	0.011*
Reintervention	-	5(14.7)	0.276 (0.15-0.49)	0.005*	4(5.5)	10(13.8)	0.11 (0.032-0.44)	0.001*

Table 4 (Cont.)

Stone-forming activity	Stone Free (%) n = 34				Residual Stone (%) n = 72			
	Protocol	Loss F/U	RR (95% CI)	P-value	Protocol	Loss F/U	RR (95% CI)	P-value
Duration of Potassium citrate use, month (mean)	59.15	-	-	-	57.53	-	-	-

* Fisher's Exact Test

Discussion

Aims of stone management are complete stone clearance, prevention of new stone recurrence and regrowth, preservation of renal function, prevention of complication, whenever the case had metabolic abnormality. At present, there are several therapies that provide better results and acceptable rate of complication. Especially, Extracorporeal Shock Wave Lithotripsy (ESWL) is widely used for kidney stone management. Following this treatment, the achievement of stone-free condition or of residual fragments shown as a therapeutic success (El-Nahas, El-Assmy, Madbouly, & Sheir, 2006) (Chongruksut et al., 2011) but also stone recurrence or regrowth still occur. In recommendation of treatments of European Association of Urology (Skolarikos et al., 2015), every patients should be assigned to a low or high-risk group for stone formation after stone passage. For correct classification, stone analysis should be done by spectroscopy or X-ray diffraction, only high-risk stone formers require specific metabolic evaluation leading to specific pharmacological treatment. At TSM Hospital, the cost of stone type investigation was expensive and impracticable in every patient; in consequence Tak protocol was designed to prevent stone recurrence and regrowth in this setting. In this study, the urine pH of samples was shown urine acid (median pH= 6.0) that may promote co-crystallisation of calcium oxalate stone. Tosukhowong et al. evaluated stone composition from four regions of Thailand (Tosukhowong et al., 2007). 80.86% were calcium oxalate stone. The most common metabolic abnormalities associated with calcium stone formation are hypercalciuria (30-60%), hyperoxaluria (26-67%), hyperuricosuria (15-46%), hypomagnesuria (7-23%) and hypocitraturia (5-29%) (Skolarikos et al., 2015). By the results of this study, we mentioned to the potassium citrate might be advantage. Unfortunately, they did not change the underlying of metabolic abnormality.

A analyzing stone-forming activity between Tak protocol and loss follow-up group, the change of the stone-free group at 60 months after intervention were 90.5% of protocol group and 9.5% of loss follow-up group. Stone free rate was 8.88 (95%CI; 2.33-33.88, p<0.001) in protocol group. Similarly to the residual stone group, protocol were 7.33 (95% CI; 1.06-50.60, p= 0.006). Stone recurrence/size increased was found in 9.5% and 84.6% of protocol and loss follow-up group respectively, which were statistically different. Similarly, Mahamoud et al. reported that 78.6% of clinical insignificant residual stone fragments cleared spontaneously within few weeks and did not recur within 5 years (Osman et al., 2005). However with long-term follow-up, residual stones led to stone recurrence and need of re-treatment in 21.4%. (Osman et al., 2005) Another study found recurrent and regrowth of kidney stone, in patient who after ESWL, were 15.5% and 25.1% in three years follow-up (Chongruksut et al., 2011). Since the patients were encouraged

and recommended for lifestyle modification and potassium citrate adjustment by urologist. Thereby the result of recurrence and regrowth among two groups might show different.

The IRR of recurrence and regrowth rates at one, two, three, four and five years were 2.97, 12.06, 7.82, 1.24 and 12.24, respectively. The IRRs were increased in the second and in the fifth years, on the other hand, Wilaiwan et al reported that after ESWL tended to have the highest stone recurrence and regrowth at first year (Chongruksut et al., 2011). A possible explanation of these results was that the patients loose of awareness in lifestyle modification after one-year stone-free period and had a problem of distance transportation.

The paradigm of kidney stone treatment was life-long due to a metabolic abnormality concerns, patients needed to appropriate long-term follow-up as well (Ramaswamy & Shah, 2014). As a consequence, the recurrence and regrowth might be found even long-term stone-free periods. The present study also found that recurrence and regrowth rate in fifth year after intervention in loss follow-up group was higher than those who with the protocol. Complication, hospitalization and reintervention at 60 months were significantly higher than those who loss follow-up. Most common complication was urinary tract obstruction that led to hydronephrosis.

There were some limitations in this study. First, the sample size was small due to a retrospective study and incomplete the data which might have no revisiting of clinical data and loss of plain film KUB, thereby the total of patients might not represent a population of stone recurrence and regrowth. Second, the spot urine pH was not a good indicator for acid-base urine status. 24-hours urine was recommended for the next study. Third, the potassium citrate was useful in patients who had calcium oxalate stone but in this study was not able to indicate the stone composition. Fourth, five years follow-up period might be sufficient to observe stone recurrence and regrowth, a longer follow-up time was recommend for the next study. Cost-effectiveness was suggested for further study.

Conclusion and Suggestions

Health education and medication adjustment are important factors of the kidney stone treatment after removal, however the recurrence of kidney stone was found in five years follow-up. Loss follow-up patients had a higher recurrence and regrowth tendency, comparison with Tak protocol patients. This protocol was able to decrease the incidence rate of stone recurrence and prevent the complication, hospitalization and reintervention. Due to lack of routine follow-up recommendation in long-term patients, this data is important for patient education and prevention strategies in the clinical practice. Every patient should be encouraged for lifestyle modification and potassium citrate adjustment in every visit. Patient's appointment after stone removal should be made more than 5 years for reducing recurrent rate.

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