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ORIGINAL PAPER

Tissue reactions of suture materials (polyglactine 910, chromed catgut and polydioxanone) on rat bladder wall and their role in bladder stone formation

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Abstract Suture materials are widely used in urological surgery especially in regions that are in contact with urine. In this study, we aimed to compare polyglactine 910, cromed catgut and polydioxanone sutures according to stone formation and inflammation, congestion and foreign body reaction that occur on bladder mucosa. Cystotomy procedure was performed, in three groups of Wistar female rats, with 4/0 polyglactine 910, 4/0 chromed catgut and 4/0 polydioxanone sutures. All groups were divided into two sub-groups with 4 and 8-week follow up periods. Rats were treated with 20 mg kg^{-1} day^{-1} Ofloxacin (i.p.) daily until the seventh post-operative day. Urinary pH, leucocyte esterase and nitrite levels were determined. All rats were killed at the end of the follow-up period and stone formation on sutures and degrees of tissue reactions (inflammation, congestion and foreign body reaction) on bladder mucosa were compared. Tissue reactions were evaluated by the same pathologist (S. K.). Chi-square and Student's *t* test were used in statistical analysis ($p < 0.05$). There was no significant difference between the mean weights of the groups. Leucocyte esterase and nitrite were negative in urine analyses. There was no significant difference between urinary pH levels of the groups with 4 and 8 weeks follow-up ($p > 0.05$). Although the difference between the degrees of congestion in groups was not statistically significant ($p > 0.05$), there were statistically significant differences between the degrees of inflammation and foreign body reaction in groups. Although the duration of urinary contact of suture is the main factor in stone formation on suture material, tissue reaction on mucosa and the physical structure of suture also affect this formation. We observed lower degrees of inflammation and foreign body reaction with 4/0 polydioxanone and no stone formation. We believe that polydioxanone may be useful and reliable in urological surgery due to these properties.

Keywords Urolithiasis · Polyglactine 910 · Polydioxanone · Chromed catgut · Surgery · Rat

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Introduction

The prevalence of urolithiasis, which has prohibitive cost due to both medical and surgical treatments, in the community, is 2–3% [1, 2]. Factors such as heredity, age, gender, geographical location, climate, nutritional status, profession and socioeconomic status play a role in the development of urolithiasis [1].

Suture materials are commonly used in urological surgery, especially for surfaces in direct contact with urine. Although absorbable suture materials are used for these

operations, encrustations on suture material and formation of stone limit the success of surgery. Additional surgical interventions can be necessary in case after the formation of these stones. Clinical observations report that all of the suture materials serve as a nucleus for the formation of stones [3–5]. Besides, absorbable suture materials lead to various levels of inflammation and foreign body reactions due to their behavior as foreign bodies in tissues [6]. Different suture materials cause various levels of inflammatory response due to their characteristic features and these culminate in varying levels of adhesions in tissues after the operation [7].

Also, because suture materials are non-self, they increase the pathogenic potentials of bacteria with low degrees of virulence in sites they occupy and may lead to infections [8].

Therefore, we aimed to compare suture materials frequently used in urological surgery (i.e. polyglactine 910, chromed catgut and polydioxanone) in terms of inflammation, congestion, foreign body reaction and stone formation on the bladder mucosa.

Materials and methods

Animals

Seventy-four female rats of Wistar strain were obtained from the Experimental Animal Breeding Program of the Faculty of Pharmaceutics of Ankara University to use in the study. The care and use of the animals were in accordance with the recommendations of the Guide for Care and Use of Laboratory Animals and ethical approval was obtained. Female rats were selected on account of their shorter urethra and ease of ruling out infravesical obstructions that may lead to formation of bladder stones. Rats were divided into groups according to suture materials used in the operations (i.e. polyglactine 910, chromed catgut and polydioxanone) and, sub-groups of 4 and 8 weeks, according to the follow-up periods; leading to six groups in total. Polyglactine 910, chromed catgut and polydioxanone sutures were used in 24, 25, and 25 rats, respectively. Twelve rats from each group were followed for 4 and the rest for 8 weeks after the operation.

Cystotomy operation procedure

Under general anesthesia with ketamine (0.225 mg/kg, i.p.) rats were fixed by their extremities. Abdominal region was entered by suprapubic median incision after appropriate sterilization, and the bladder was freed from neighboring structures, while attention was paid to prevent harm to vasculature. A cystotomy incision of approximately was performed 1 cm on the apex of the bladder. This incision was closed by 4/0 polyglactine 910, 4/0 chromed catgut or 4/0 polydioxanone, according to the groups of rats. After, heamostasis surgical intervention was terminated by closing the skin and muscle by 3/0 chromed catgut. Weights of all of the rats were recorded prior to the operation.

Post-operative follow up

20 mg kg^{-1} day^{-1} of i.p. Ofloxacin was applied to each group of rats promptly at the end of the operation and for during 7 days follow-up. All groups of rats were placed in separate cages and unlimited fodder and water were supplied during the study period. Rats were followed in the Animal Care Unit of the Pharmaceutics Faculty of Ankara University, under 55–60% relative humidity and 20°C room temperature.

Urine analysis

Urinary pH, leukocyte esterase and nitrite levels of each rat was determined and recorded prior to the surgical intervention, after the antibiotic treatment and just before sacrificing via Uritest® 10 U urine analysis sticks.

Macroscopic stone analysis and pathological evaluation

Rats were sacrificed by means of CO_2 asphyxiation at the end of follow-up periods. Bladder was reached in sacrificed animals via suprapubic median incision. Later, it was freed from neighboring tissues and removed by a circumnavigating incision through the bladder neck. After the bladder opening by an incision to the posterior wall and the structure of the suture, the encrustation, and macroscopic stone formation was evaluated. After this procedure, cystotomy line was prepared for pathological evaluation. Throughout the procedures a loop with 2.5× magnification was used.

Pathological evaluations were done by the same pathologist (S. K.), by using hematoxylin–eosine stain, under light microscope. Inflammation, congestion and foreign body reaction in the bladder tissue around the suture was investigated and graded (Table 1).

Statistical evaluations

The three suture groups were compared among themselves and each group was compared within itself for the duration of follow-up (i.e. 4 and 8 weeks), for levels of inflammation, congestion and foreign body reaction by using chi-square test. Difference in stone formation in between suture groups was also investigated by using chi-square test. Statistical evaluations for urinary pH analyses were done by

Table 1 Grading of pathological findings at the cystotomy anastomosis line

Inflammation	
First degree	No/mild inflammation around the suture material
Second degree	Moderate/severe inflammation around the suture material
Congestion	
First degree	Congested vessels are haphazardly distributed
Second degree	Focal or globally increased numbers of congested vessels
Foreign body reaction	
First degree	Mild histiocytic infiltration and few giant cells around the suture material
Second degree	Multinucleated giant cells surrounding the suture material at some places or in multiple groups

Student's *t* test and one-way ANOVA was used for comparing weights.

Results

No complications due to operation or method of anesthesia were noted during the post-operative period in rats enrolled in the study. In total, 36 rats from all of the groups were sacrificed at the fourth week, while the remaining 38 were sacrificed at the eighth week.

Mean body weights of rats in polyglactine 910, catgut and polydiaoxanone groups were 246.1 ± 25.5, 239.3 ± 23.4 and 249.1 ± 25.2 g, respectively and no statistically significant difference was noted ($p = 0.367$).

None of the rats were tested positive for either urine leukocyte esterase or nitrite. No statistically significant difference was observed when urinary pH was evaluated preoperatively and prior to the scarification for each of the suture groups and in between follow-up periods ($p > 0.05$).

Seven cases of macroscopic bladder stone formation on the line of anastomosis were noted in rats whose bladders were opened at the end of the fourth week, one in the polyglactine 910 group (8.3%) and the rest comprised 50% of the chromed catgut group; whereas two cases were noted in rats which were followed for 8 weeks, one in the polyglactine 910 group (8.3%) and the other in the chromed catgut group (7.7%). None of the rats in which polydioxanone suture was used developed macroscopic stones, in both follow-up periods (Table 2). The suture groups differed statistically significant for macroscopic stone formation ($p = 0.01$).

When, the bladder tissues were evaluated at the end of 4 and 8 weeks follow-up there was a statistically significant difference between suture groups in terms of inflammation and foreign body reactions (respectively; $p = 0.005$, Fig. 1 and $p = 0.033$, Fig. 3). And no significant difference between the groups for levels of congestion was noted ($p = 0.449$, Fig. 2).

Distribution of all suture groups according to inflammation, congestion and degree of foreign body reaction at the end of 4 and 8 weeks has been shown in Table 3.

Table 2 Distribution of macroscopic stone formation

Suture groups	Stone formation/total (%)		Total number of stone formation	Number of total rats
	End of 4 weeks*	End of 8 weeks		
Polyglactin 910	1/12 (8.3)	1/12 (8.3)	2 (8.3%)	24
Chrome catgut	6/12 (50)	1/13 (7.7)	7 (28%)	25
Polydioxanone	0/13 (0)	0/12 (0)	0 (0%)	25
Total	7/37 (18.9)	2/37 (5.4)	9 (12.1%)	74

* Chi square test; $p = 0.01$

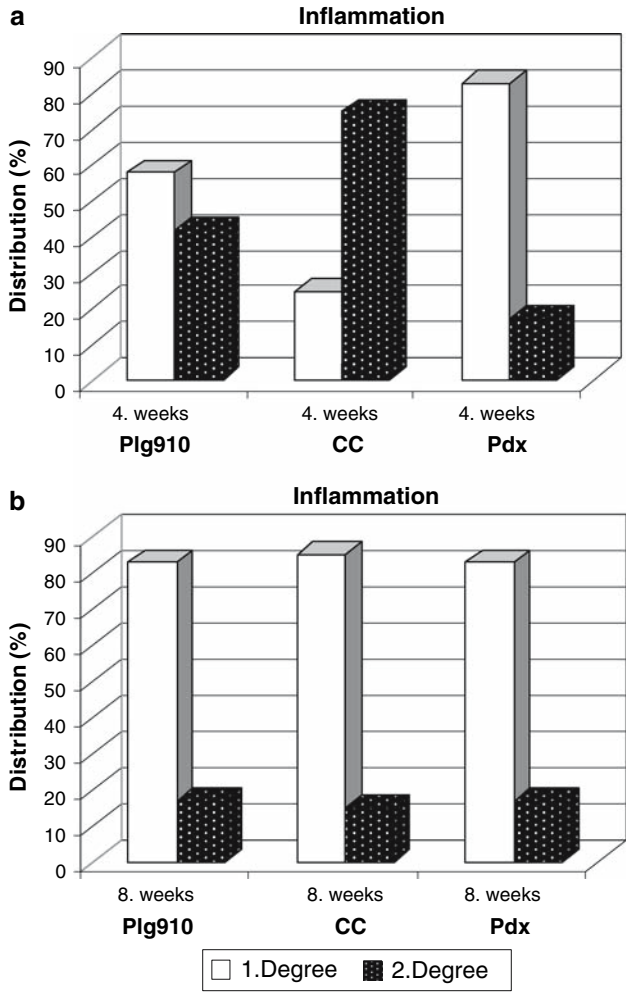

Fig. 1 Relationship between degree of inflammation and time. **a** At the end of 4 weeks, **b** at the end of 8 weeks

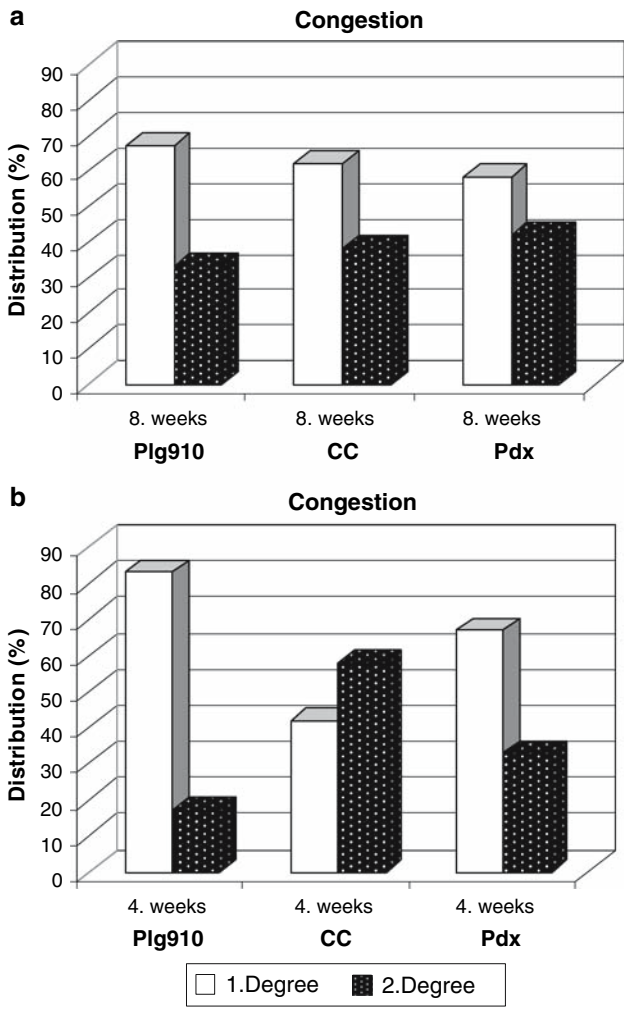

Fig. 2 Relationship between degree of congestion and time. **a** At the end of 4 weeks, **b** at the end of 8 weeks

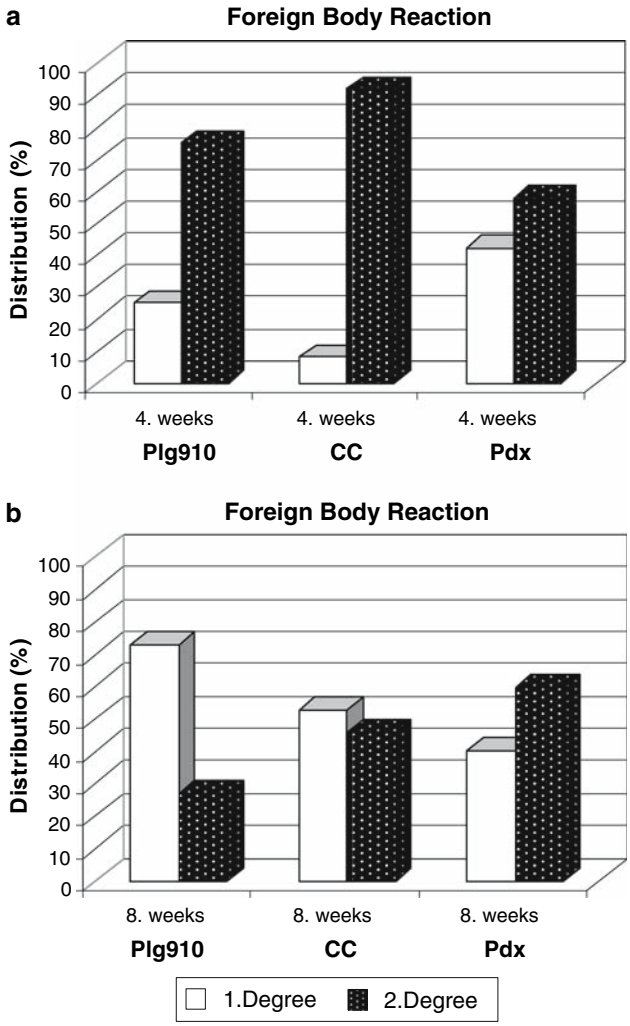

Fig. 3 Relationship between degree of foreign body reaction and time. **a** At the end of 4 weeks, **b** at the end of 8 weeks

Discussion

Absorbable suture materials are frequently preferred in open surgical procedures of the urinary system. One of the determinants in this choice is decreased morbidity due to stone formation in the urinary system either due to encrustation on the suture material or macrocalcules [9, 10]. Suture materials act as foreign bodies in the urinary system and lead to crystallization and calcification in time due to their direct contact with urine. This phenomenon decreases the success of the surgical procedure and increases morbidity due to obstruction and secondary infection [11, 12].

However, materials may vary in terms of inflammation, foreign body reaction and congestion produced in tissues and this may determine the healing process.

Therefore, we have investigated the tissue reaction, crystallization and stone formation characteristics of chromed catgut, polyglactine 910 and polydioxanone in rat bladders, which are frequently used, absorbable sutures in open surgeries of the urinary system. According to previous studies investigating the behavior of suture materials within the urinary system, factors such as suture diameter, presence of infection, urinary pH and duration may be important [13]. Therefore, we have used 4/0 suture materials uniformly throughout groups to close cystotomy and antibiotic therapy was applied to prevent infection. For prophylaxis, 20 mg kg^{-1} day^{-1} i.p. ofloxacin was applied to rats for 7 days [14].

When pH levels were compared between groups according to suture materials and duration of follow-up, no significant differences between groups emerged. This finding was in accordance with those reported in the study conducted by Stewart et al. [15].

As demonstrated in the study by Flanagan et al. [16], 95% of urinary infections can be determined by means of urinary leukocyte esterase and nitrite determination. Therefore, we

Table 3 Distribution of suture groups according to inflammation, congestion and foreign body reaction degree at the end of 4 and 8 weeks

Time	Inflammation				Congestion				Foreign body reaction			
	1°		2°		1°		2°		1°		2°	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Polyglactine 910												
4 weeks	7	58.3	5	41.7	10	83.3	2	16.7	3	25	9	75
8 weeks	10	83.3	2	16.7	8	66.7	4	33.3	8	72.7	3	27.3
Chromed catgut												
4 weeks	3	25	9	75	8	61.5	5	38.5	1	8.3	11	91.7
8 weeks	11	84.6	2	15.4	5	41.7	7	58.3	7	53.8	6	46.2
Polydioxanone												
4 weeks	10	83.3	2	16.7	8	66.7	4	33.3	5	41.7	7	58.3
8 weeks	10	83.3	2	16.7	7	58.3	5	41.7	4	40	6	60
	0.005*				0.449				0.033*			

* Chi square test; $p < 0.05$

ruled out the presence of infection by evaluating leukocyte esterase and nitrite in the urine of rats. After homogenizing the groups in terms of urinary pH and development of infection, we have compared the findings of inflammation, congestion, foreign body reaction and macroscopic calcification produced by different groups of sutures.

A previous study in which polydioxanone, polyglactine 910 and chromed catgut was used reported that the findings of inflammation was highest in the polydioxanone group at the first week but decreased from the fourth week and progressed similarly to the other groups until sixth month [15]. Similar to that study, we have found the lowest level of inflammation in the polydioxanone group at the fourth week proceeded low.

Hanke et al. [13], reported that the highest inflammatory response was in the chromed catgut group at the seventh week in their rabbit model (which was used on account of its similarity with humans). Similar to these reports, severe inflammatory findings in the polyglactine 910 group in our study was found to be more frequent at the end of the fourth week than at the end of the eighth week. Inflammatory responses which did not change in time were found to be lower especially at the first term and continued to be similar at the eighth week in the polydiaxanone group which was expected to be absorbed in a longer duration of time.

Our results on vessel congestion in catgut group (Table 3) was similar to those reported by Bakkum et al. [11]. In this study, catgut, polypropylene and polyglactine 910 suture materials were compared in terms of post-operative adhesion and inflammatory response developed around the suture and no significant difference was found in the number of vessels determined microscopically around the sutures [11].

Because increase in congested vessels provides cellular elements and mediators needed for inflammatory response against the suture material, increased number of vessels in tissues with a higher level of inflammatory response can be expected. Though an increase in the number of congested vessels on short term in the chromed catgut group, which also displayed a more severe foreign body reaction and inflammation was noted in our study, this did not reach significance.

Histiocyte infiltration and giant cell dispersion around the suture materials were used in evaluation of the foreign body reaction in our study. Hanke et al. [13] used a similar method in their rabbit model and reported that foreign body reaction was related with the duration of suture absorption, developing at the end of the absorption process. They also noted that suture diameter may be important in this process.

Hanke et al. [13] reported that polyglactine 910 was absorbed homogenously in the tissue. This observation was supported by numerous studies [17, 18]. Due to the demonstration of lower foreign body reactions when compared to plain catgut, chromed catgut and non-absorbable sutures, using polyglactine 910 in urinary system surgery was recommended [13]. Our results also support this recommendation.

Polydioxanone which has a lower rate of foreign body reaction when compared to polyglactine 910 in early stages emerges with higher rates of foreign body reaction in further stages. However, it should be borne in mind that polydiaxanone is absorbed in a longer duration of time and its advantages and disadvantages should be accordingly evaluated. Also, the finding that no stone formation was observed in the polydioxanone group underlines potential advantages.

Macroscopic stone formation on the suture material following urological operations using dense suture materials is one of the problems arising in general urological practice [19, 20]. Previous studies conducted on rats, rabbits and other animals tried to address this problem [12, 15, 21].

A higher frequency of stone formation for polypropylene, which is a non-absorbable suture, was reported and this observation was explained in terms of longer duration of contact with urine [12]. This report, which is relatively earlier, was noted a moderate degree of stone formation with polydiaxanone and the lowest degree with chromed catgut [12]. In accordance with these observations, the use of non-absorbable sutures in urinary system surgery is reduced.

Stewart et al. [15] found no difference in stone formation between chromed catgut, polyglactine 910 and polydioxanone. This study reported no macroscopic stone formation in the polydioxanone group, though microscopic calcifications arising at the end of a follow-up period of up to 6 months [15]. Contrary to our results, Morris et al. [12] reported a lower macroscopic stone formation in the chromed catgut group, however they used a rabbit model and rabbits have an elevated risk for stone formation on account of their more alkaline and hence, more calculogenic urine.

Lots of studies investigating the usage of sutures in the genitourinary system and analyzing development of encrustation and stone formations on sutures reported, increased formation of stones with plain catgut [9, 17, 18], polyglactine 910 [22, 23], or polypropylene [10, 24], which is a non-absorbable suture. Other studies reported mild differences between suture materials used [12, 15]. We have found that 77.7% (7 out of 9 stones) of stones occurred on chromed catgut while 22.3% (2 out of 9 stones) on polyglactine 910. No macroscopic stone formation was noted on polydioxanone throughout the study period and the difference between groups was statistically significant.

Some studies posit that epithelial covering of the suture material may prevent against encrustation [22]. However, stone formation on longer term may occur in some studies. This may be explained by a diminutive urothelial defect developing in the formerly epithelized material and subsequent stone formation [13]. Trevino et al. [25] report a stone formation developing 1–2 years after a bladder surgery in which polypropylene was used. They hypothesize that this may be due the migration of non-absorbable suture from the tissue to the lumen with time. However, the majority of stones found in our study were diagnosed at the end of a 4-week follow-up.

There were statistically significant differences between the degrees of inflammation and foreign body reaction in groups. We observed lower degrees of inflammation and foreign body reaction with 4/0 polydioxanone and no stone formation.

Considering our results, it may be prudent to declare that polydioxanone, which leads to a milder tissue reaction and does not seem to increase stone formation, may be advantageous as a monofilament suture material in urologic surgical procedures.

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