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URINE CYTOKINE PROFILE AND NEPHROPROTECTIVE EFFECT OF LERCANIDIPINE IN PATIENTS WITH UROLITHIASIS WITH OBSTRUCTIVE UROPATHY BEFORE AND AFTER NEPHROSTOMY

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Objective. To study the nephroprotective effect of lercanidipine and its influence on creatinine clearance and cytokine damage in patients with urolithiasis with obstructive uropathy. **Material and methods.** Of 96 patients evaluated, 66 were diagnosed with kidney stones in the ureteropelvic segment and obstructive uropathy, which was then treated with percutaneous nephrostomy. All 66 patients were given antibacterial and anti-inflammatory therapy to prevent postoperative infections, but in addition, 33 were treated with lercanidipine, 10 mg per day. IL-8, VEGF, MCP-1, G-CSF, and GM-CSF concentrations in the urine were determined by solid-phase ELISA. The estimated glomerular filtration rate was calculated using the CKD-EPI formula. All studies were done preoperatively and on days 7, 14, 21, and 28 after nephrostomy. A control group consisted of 30 people with kidney stones without sings of obstruction. **Results.** In the patients with obstructive uropathy, a correlation was found between VEGF, IL-8, and MCP-1 concentrations in the urine and the serum creatinine and estimated glomerular filtration rate. Patients in the lercanidipine group had a faster decrease in IL-8, VEGF, MCP-1, and GM-CSF concentrations in the urine and improved renal function compared with patients who did not receive lercanidipine. By day 21 after nephrostomy, the lercanidipine group had values comparable with the control group, whereas the group not treated with lercanidipine did not achieve similar values until day 28. **Conclusion.** The third generation calcium channel blocker lercanidipine is nephroprotective in patients with obstructive uropathy.

Keywords: cytokine profile; urine; obstructive uropathy; nephroprotection; lercanidipine.

ЦИТОКИНОВЫЙ ПРОФИЛЬ МОЧИ И ОЦЕНКА НЕФРОПРОТЕКТИВНОГО ЭФФЕКТА ЛЕРКАНИДИПИНА У БОЛЬНЫХ УРОЛИТИАЗОМ С ОБСТРУКТИВНОЙ УРОПАТИЕЙ ДО И ПОСЛЕ НЕФРОСТОМИИ

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Цель исследования — изучение нефропротективного эффекта лерканидипина, влияние его на динамику клиренса креатинина и уровня цитокинов повреждения у больных мочекаменной болезнью с наличием обструктивной уропатии при дренировании почки. **Материал и методы.** В исследование были включены 96 пациентов, из которых у 66 были диагностированы конкременты лоханочно-мочеточникового сегмента и нарушение оттока мочи из почки. Всем 66 больным с признаками обструкции выполняли чрескожное дренирование почки (нефростомия). Пациентам 1-й группы (n = 33) для предотвращения развития инфекционных осложнений

в послеоперационном периоде проводили антибактериальную и противовоспалительную терапию. Больным 2-й группы (n = 33) дополнительно назначали лерканидипин в дозе 10 мг в сутки. У всех наблюдаемых больных определяли концентрацию IL-8, VEGF, MCP-1, G-CSF и GM-CSF в моче методом твердофазного ИФА, по формуле CKD-EPI рассчитывали скорость клубочковой фильтрации. Все исследования выполняли на дооперационном этапе, а также на 7, 14, 21 и 28-е сутки после дренирования почки. Группу сравнения составили 30 человек с конкрементами чашек и без признаков обструкции. **Результаты.** У больных с обструктивной уропатией выявлена корреляционная связь между содержанием VEGF, IL-8, MCP-1 в моче и уровнем сывороточного креатинина и величиной СКФ. У пациентов 2-й группы, получавших лерканидипин, отмечалось более быстрое снижение содержания IL-8, VEGF, MCP-1, GM-CSF в моче и улучшение показателей почечной функции по сравнению с больными 1-й группы. Достижение значений группы сравнения у больных 2-й группы достигалось к 21-му дню после дренирования, а у пациентов 1-й группы — к 28-му дню. **Заключение.** Блокатор кальциевых каналов третьего поколения лерканидипин может быть использован в качестве средства нефропротективной терапии в комплексном лечении больных с обструктивной уропатией.

Ключевые слова: цитокиновый профиль; моча; обструктивная уропатия; нефропротекция; лерканидипин.

INTRODUCTION

Patients with urolithiasis in the presence of different degrees of obstruction in the urinary tract have a high risk for complications, which includes calculous pyelonephritis [1, 2]. Development of obstructive uropathy (OU) is usually accompanied by structural and functional changes in the renal parenchyma. This impairment predominantly affects the tubulointerstitial tissue and is associated with a reduction in renal function [3]. It has been previously established that even a small sized concretion with obstruction may have a significant influence on renal function and clinical manifestation of the disease [4].

Despite the active development of endoscopy-assisted and percutaneous surgical approaches for treatment of urological patients with urolithiasis and obstructive syndrome, there are clinical conditions which require appropriate kidney drainage at the first stage. Delayed treatment of OU may cause tubular atrophy, interstitial fibrosis, and inflammation accompanied by excessive production of a variety of cytokines and mediators. Measuring the change in urine biomarker levels can monitor the severity of structural and functional damage. The risk for kidney diseases increases with chronic OU, which may eventually lead to patient disability. Prior to the development of subsequent complications, OU has no apparent clinical manifestation in the majority of cases but is accompanied by tubular and glomerular damage.

The current established standard of nephroprotective therapy is based on angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARB) [5]. New studies provide data showing the nephroprotective effect of new-generation calcium channel blockers (CITATION). Studies of the new-generation drug lercanidipine demonstrate a significant nephroprotective effect (CITATION). A marked decrease in intraglomerular pressure with persistent vasodilation of not only afferent (as in traditional calcium channel blockers), but also efferent (as in ACE inhibitors and ARBs) glomerular arterioles has now been determined (CITATION). Calcium channel blockers (lercanidipine and others) significantly decrease intraglomerular pressure, slowing renal damage [6]. The mechanism of the efferent vasodilation in the presence of the new-generation calcium channel blockers is not yet clear. Specific roles are assigned to vasodilators produced by the vascular endothelium, namely nitric oxide and prostaglandin II. Recent findings show that blockade of T-type calcium channels inhibit prostaglandin II production, causing subsequent vasodilation of efferent arterioles.

Renal parenchyma damage caused by OU initiates a cascade of molecular interactions with several morphological changes, which have triggered several investigations to discover agents to protect or at least limit the extent of structural and functional renal damage and help influence on restoration rate. The current literature is quite focused on the search of urinary markers in patients with pyelonephritis and urolithiasis for the assessment of inflammatory changes [7–11] and also to estimate the severity of acute renal damage [12–14]. However, there is a growing need for studies on easily extracted markers in urine, which can characterize the degree of renal function restoration.

The aim of this research was to study the nephroprotective effect of lercanidipine and its influence on IL-8, vascular endothelial growth factor (VEGF), MCP-1, G-CSF and GM–CSF levels, and creatinine clearance in urolithiasis patients with OU.

MATERIALS AND METHODS

We recruited 96 urolithiasis patients treated in 2015–2017 in the Mirotvortsev S.R. clinic in the VI Razumovsky Saratov State Medical University. Before enrollment in the study, each patient provided written, informed consent. Enzyme immunoassays of the above-mentioned markers were performed according to symptoms and medical history. All patients had a physical examination, complete blood count and chemistry, urine test, plain kidney and urinary tract X-ray, excretory urography, ultrasonography, and multispiral computer tomography with image reconstruction. Group 1 included 33 patients with concretions from 1.0 to 2.0 cm in size located in the ureteropelvic segment. The average age of patients in group 1 was 45.8 years (range: 25 to 60 years). According to X-ray and ultrasonography, all patients in group 1 had signs of upper urinary tract obstruction, with the size of renal calyces varying from 6 mm to 10 mm, renal pelvis – 1.8–3.5 cm, as well as unilaterally reduced excretory renal function as assessed by excretory urography. The duration of obstruction (time from onset of renal colic) ranged from 1.5 to 12 weeks. However, there were no signs of hyperthermia or other symptoms of active pyelonephritis in this period. Enrolled patients had a decreased GFR of 30 to 60 ml/min. Group 2 included 33 patients with a similar clinical picture, age, distribution of sex, and clinical characteristic data. In both groups, standard nephrostomy was performed in the operative room using the surgical set for percutaneous nephrostomy before lithotripsy. All patients were given antibacterial and anti-inflammatory therapy in the postoperative period, but in addition, 33 were treated with lercanidipine, 10 mg per day for 1 month for nephroprotection. The second step of treatment (lithotripsy) was performed on days 28–35 after nephrostomy. A control group had 30 patients with calyceal concretions 1 cm to 1.5 cm in size but without obstruction, with age and sex similar to the treatment groups.

We measured VEGF, MCP-1 (Monocyte Chemoattractant Protein 1), IL-8 (Interleukin-8), G-CSF (Granulocyte-colony stimulating factor), and GM–CSF (Granulocyte-macrophage colony-stimulating factor) in the urine of patients in treatment groups five times. The first urine sample was taken during the renal pelvic puncture. The urine was collected into a special container which was previously injected with preservative ProClin 300, 20 mcL (SUPELCO, USA) and capped. The following urine samples were obtained on days 7, 14, 21, and 28 after nephrostomy from a nephrostomic drainage. In the control group, a single urine sample was taken. Cytokine concentrations in urine were determined by solid-phase ELISA using Vektor-Best panel (Novosibirsk). In patients with OU, blood samples to measure creatinine levels and urine samples were obtained simultaneously (blood samples from patients in the control group were taken once). The serum creatinine level was used for calculation of GFR using the CKD-EPI formula for Europeans.

Statistical data analysis was performed by Statistica 10.0, SPSS13.0 software (COMPANY, CITY, STATE). There was no normal distribution of values in the series, and therefore we used nonparametric statistical methods including median, interquartile range, and box plots. A nonparametric Mann–Whitney U test was used to test for differences between two independent groups. The level of significance for all statistics was defined as $p < 0.05$. To assess diagnostic utility for urine markers, a characteristic curve (ROC analysis) was created.

RESULTS

In groups 1 and 2, there was a nearly 2-fold increase in VEGF, MCP-1, and IL-8 concentrations, 1.4-fold for GM–CSF and 7.9-fold for G-CSF compared with the control group (Table 1, PVALUE). There was no significant difference between treatment groups.

To assess the diagnostic utility for these markers, ROC analysis was performed (Fig. 1). The diagnostic utility was determined for VEGF (sensitivity – 95.2%, specificity – 95%), IL-8 (sensitivity – 83.9%, specificity – 85%), MCP-1 (sensitivity – 87.1%, specificity – 95%), GM–CSF (sensitivity – 87.1%, specificity – 85%), and G-CSF – 5.89 pg/ml (sensitivity – 77.3%, specificity – 90%).

Resolving the obstruction caused a significant decrease in VEGF, MCP-1, IL-8, GM–CSF levels in the urine. Change of marker levels are shown in Figure 2–5 (X-axis – days, Y-axis – marker concentration, pg/ml; red curve – the group 1, green curve – the group 2, blue curve – the control group).

After nephrostomy, we observed decreased levels of VEGF down to values similar to the control group by day 28. However, for lercanidipine, urine VEGF levels decreased faster and reached the values similar to control as early as day 21 (see Fig. 2).

Such tendency was also observed in urine MCP-1 levels in patients with OU (Fig. 3). A gradual decrease in MCP-1 level was determined after nephrostomy in patients with OU. Moreover, the lercanidipine group had a more rapid decrease in MCP-1. By day 21 after nephrostomy, the patients who received lercanidipine had values comparable to the control group.

While resolving the obstruction, we observed a gradual decrease of urine IL-8 levels in both patient groups, reaching levels comparable to the control group by day 21 in the lercanidipine group and by day 28 in patients who did not receive lercanidipine (Fig. 4).

After nephrostomy, patients with OU had an increase in urine GM–CSF concentration, with the peak by day 14 and following decrease of marker levels. In addition, the levels in patients without lercanidipine reached the control values by day 28 and in patients who received lercanidipine as early as by day 21.

For urine G-CSF concentrations, there was no significant correlation with time from nephrostomy in both groups of patients.

Assessment of renal function in both groups before nephrostomy showed an increase of serum creatinine up to 140±10.6 mcmol/l and a decrease in GFR up to 55±13.3 ml/min. After restoration of urine drainage from the kidney, the levels of these parameters became normalized, with a more rapid improvement in patients who received lercanidipine as nephroprotector (Fig. 6).

Correlations between levels of urine markers and serum creatinine and GFR are shown in Table 2. Correlations between urine VEGF, IL-8, MCP-1, and serum creatinine, and GFR were determined.

DISCUSSION

Even without apparent clinical manifestation, unilateral OU is associated with tubular and glomerular damage. Urine stagnation causes an increase of intraurethral and intrapelvic pressure, renal blood flow alteration, and mechanical tension of renal tubules [15]. This process is accompanied by activation of tubulocytes and vascular endothelial cells which

Table 1

Preoperative median concentrations of urine markers in patients with obstructive nephropathy and a control group

Marker (pg/ml)	Urine *Me* (25–75%)		
	Control group, *n* = 30	Group 1, *n* = 33	Group 2, *n* = 33
VEGF	231.9 (198.8–242.1)	539.5 (454–546.5)	524.34 (387–546.4)
IL-8	20.6 (19–23.55)	43.5 (38.2–45)	43.7 (32.8–45.8)
MCP-1	320.5 (295.9–338)	641.22 (568.9–650)	647 (425.6–709.6)
G-CSF	0 (0–3.15)	7.99 (6.78–9.8)	7.98 (5.6–11.23)
GM-CSF	5.3 (3.75–5.6)	7.35 (6.6–8.3)	7.35 (7.02–7.86)

Note. $p > 0.05$ between the groups 1 and 2; $p > 0.05$ between the treatment groups and control group for all markers.

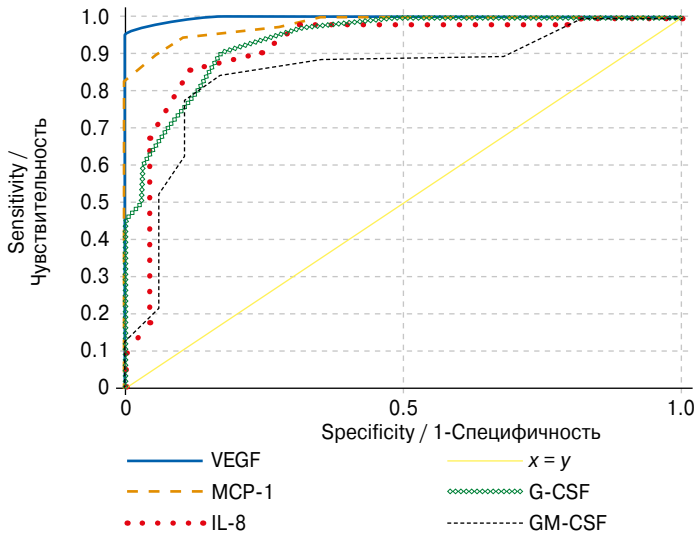


Fig. 1. ROC curves to assess sensitivity and specificity for urine VEGF, MCP-1, IL-8, G-CSF, GM-CSF concentrations in patients with urolithiasis and obstructive uropathy

Рис. 1. ROC-кривые чувствительности и специфичности VEGF, MCP-1, IL-8, G-CSF, GM-CSF в моче в оценке обструктивной уропатии у больных нефролитиазом

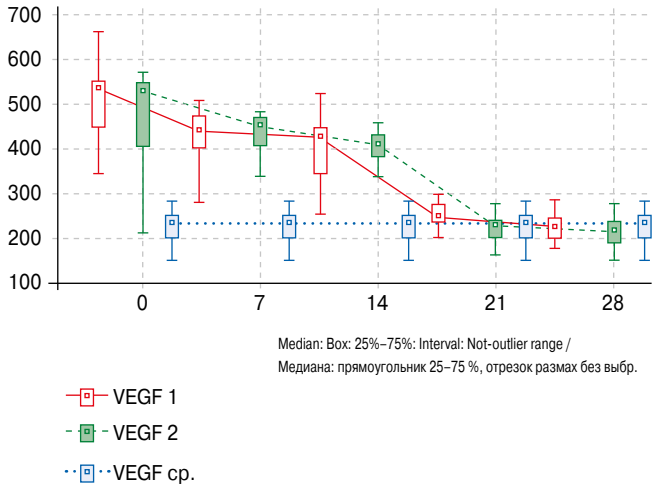


Fig. 2. Change of urine VEGF levels in patients with obstructive uropathy in the first month after nephrostomy and in controls
Рис. 2. Изменение активности VEGF в моче больных с обструктивной уропатией в течение месяца после дренирования почки и группы сравнения

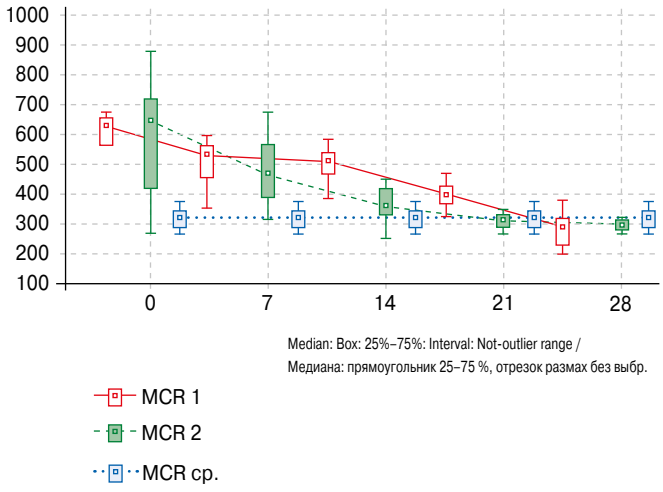


Fig. 3. Change of urine MCP-1 levels in patients with obstructive uropathy in the one month after nephrostomy and in controls
Рис. 3. Изменение активности MCP-1 в моче больных с обструктивной уропатией в течение месяца после дренирования почки и группы сравнения

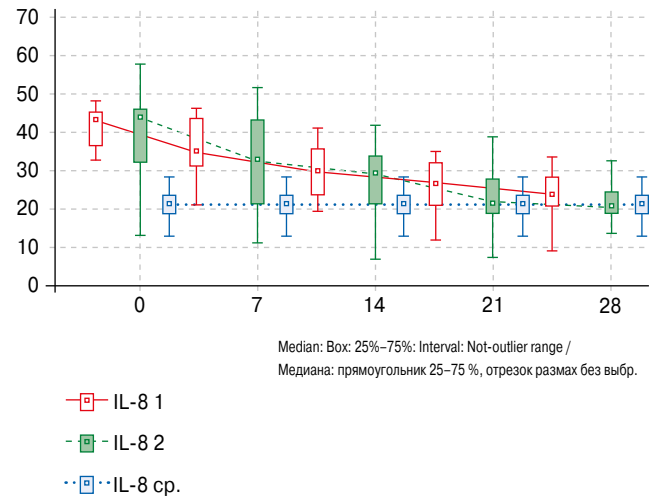


Fig. 4. Change of urine IL-8 levels in patients with obstructive uropathy in the one month after nephrostomy and in controls
Рис. 4. Изменение активности IL-8 в моче больных с обструктивной уропатией в течение месяца после дренирования почки и группы сравнения

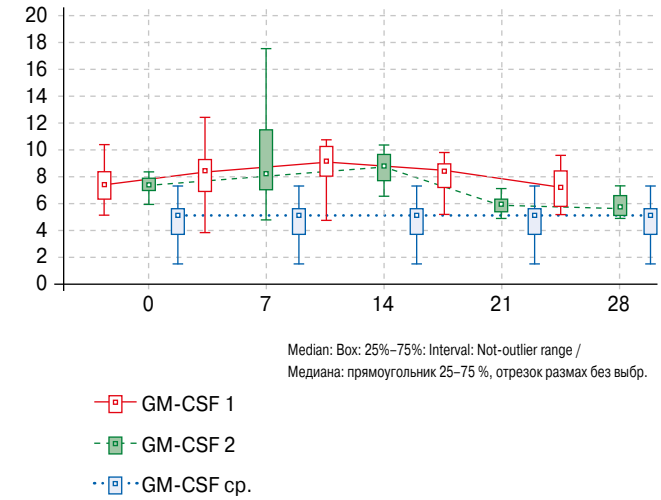
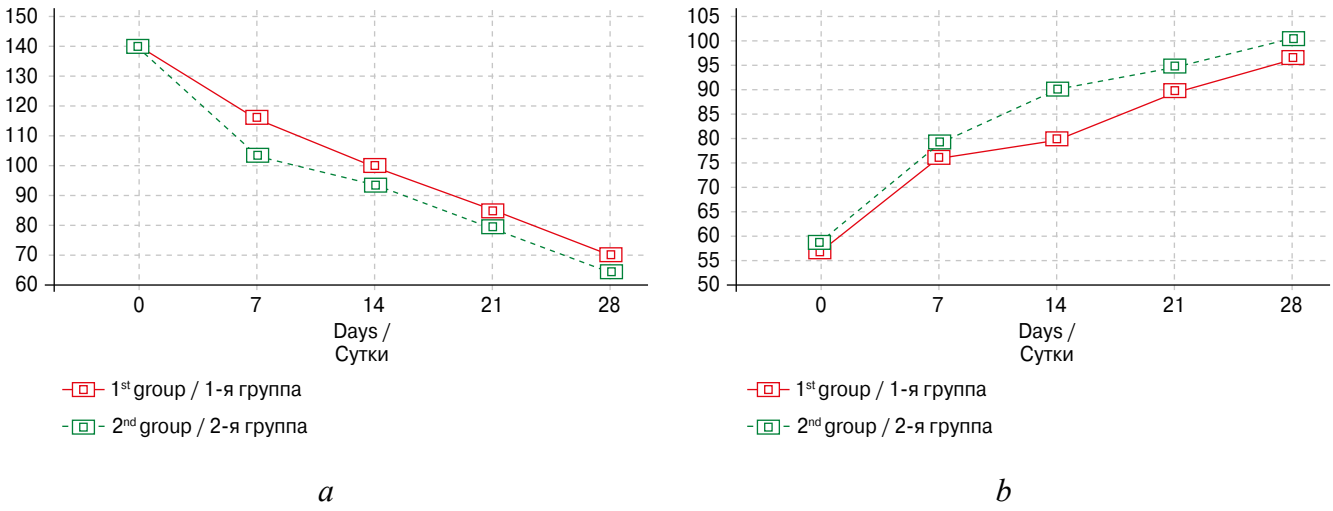


Fig. 5. Change of urine GM-CSF levels in patients with obstructive uropathy in the one month after nephrostomy and in controls
Рис. 5. Изменение активности GM-CSF в моче больных с обструктивной уропатией в течение месяца после дренирования почки и группы сравнения

produce a variety of pro-inflammatory cytokines and chemokines, initiating migration of neutrophil, leukocyte, and macrophages to the damaged interstitial tissue and to form inflammatory infiltrates. One of the main factors promoting its formation is MCP-1, which is produced by activated tubulocytes and regulates the migration of monocytes/macrophages to the inflammation area. Interleukin-8 (IL-8) is released by macrophages and endothelial cells and is involved in maintaining chronic inflammation, plays the same significant role in this process. It has been demonstrated that production of this chemokine increases in unilateral obstruction associated with urodynamic alteration and local inflammation. Development of OU leads to remodeling of blood flow and tissue hypoxia which induces an increase of VEGF production in glomerular podocytes and tubular cells [16]. Additionally, GM–CSF is produced by tubulocytes and contributes to monocyte survival and macrophage activation. Production of this cytokine increases with the development of OU. One more cytokine which has been observed in patients with OU is granulo-



a *b*

Fig. 6. Renal function in patients with obstructive uropathy before and after nephrostomy by treatment group. *a*: creatinine level (μmol/L); *b*: eGFR by CKD-EPI (mL/min)
Рис. 6. Функциональное состояние почек у больных с обструктивной уропатией 1-й и 2-й групп до и после дренирования почки: *a* — уровень креатинина (мкмоль/л); *b* — СКФ CKD-EPI (мл/мин)

Table 2

Correlation between levels of urine biomarkers and renal function parameters

Renal function parameters	Molecular markers				
	VEGF	MCP-1	IL-8	G-CSF	GM–CSF
Serum creatinine	$r = 0.51$	$r = 0.511$	$r = 0.375$	$r = -0.05$	$r = 0.266$
GFR (CKD-EPI)	$r = -0.551$	$r = -0.602$	$r = -0.381$	$r = 0.032$	$r = -0.19$

cyte-colony stimulating factor (G-CSF). This factor activates growth and differentiation of hematopoietic cells, in particular granulocytes, macrophages, and eosinophils, and also stimulates neutrophil chemotaxis [17]. Resolution of obstruction and subsequent restoration of appropriate urodynamics provide a decrease in intrapelvic pressure and reduces the traumatic effect on renal tubules in decreasing the production of these inflammatory markers. Reducing these markers down to the level of the control group indicates a completion and resolution of these pathological processes and thus suggests a possibility for second stage surgical treatment. In addition, this aims to minimize risks of complications, such as active pyelonephritis and long-term renal fibrosis. Our results of reduced urine VEGF, IL-8, MCP-1, GM–CSF levels on day 28 after obstruction should be considered as optimal terms for lithotripsy in patients with OU without lercanidipine therapy. Lercanidipine therapy promotes a more rapid restoration of renal function and decrease of cytokine levels. Considering the improvement in these marker levels, the administration of lercanidipine is preferred after nephrostomy. However, lercanidipine efficacy was not studied in patients with unresolved obstruction. Lercanidipine therapy reduces terms for lithotripsy by day 21 after nephrostomy.

Therefore, lercanidipine therapy restores renal function in urolithiasis patients with OU after nephrostomy, through the rapid decrease in inflammatory and angiogenesis markers, renal fibrosis and colony-stimulating factors, correlating with a decrease in serum creatinine levels and increased GFR. We recommend lercanidipine as a nephroprotector in this particular group of patients. At the recommended dose of 10 mg per day for 3–4 weeks, lercanidipine may reasonably reduce the waiting period before the second stage of surgical treatment, which then offers a reduction in the total duration of treatment and optimization of urological flow.

CONCLUSION

1. The calcium channel blocker lercanidipine may be used as nephroprotector during the resolution of obstruction for treatment of urolithiasis patients. The data suggest that lercanidipine (at a dose of 10 mg per day) may be recommended in patients with urolithiasis to reduce terms for renal drainage prior to lithotripsy.

2. Urine mediator levels (VEGF, MCP-1, IL-8), correlate with GFR values and may be used as non-invasive indices for assessment of structural and functional changes of the renal parenchyma in urolithiasis patients with OU.

REFERENCES

1. Hasna A, Meiyappan K, Periyasam SG, et al. Is urolithiasis associated with increased levels of high sensitivity C-reactive protein and interleukin-6 in diabetic patients? *J Clin Diagn Res*. 2015;9(3):1-3. doi: 10.7860/JCDR/2015/12489.5681.
2. Wang CJ, Hsu CS, Chen HW, et al. Percutaneous nephrostomy versus ureteroscopic management of sepsis associated with ureteral stone impaction: a randomized controlled trial. *Urolithiasis*. 2016;44(5):415-419. doi: 10.1007/s00240-015-0852-7.
3. Ucero AC, Gonçalves S, Benito-Martin A, et al. Obstructive renal injury: from fluid mechanics to molecular cell biology. *Open Access J Urol*. 2010;2:41-55.
4. Arakawa T. Surgical management for urolithiasis. *Clin Calcium*. 2011;21(10):1535-1541. (In Japanese). doi: CliCa111015351541.
5. Николаев А.Ю. Возможности и перспективы нефропротективной стратегии // Терапевтический архив. – 2012. – № 6. – С. 77–80. [Nikolaev AYu. Vozmozhnosti i perspektivy nefroprotektivnoj strategii. *Terapevticheskij arhiv*. 2012;(6):77-80. (In Russ.)]
6. Кукес В.Г., Остроумова О.Д., Стародубцев А.К. Антагонисты кальция: современные аспекты применения в кардиологии // Consilium medicum. – 2006. – № 11. – С. 113–117. [Kukes VG, Ostroumova OD, Starodubtsev AK. Calcium antagonists: modern aspects of the use in cardiology. *Consilium medicum*. 2006;(11):113-117. (In Russ.)]
7. Глыбочко П.В., Захарова Н.Б., Понукалин А.Н., и др. Диагностическое значение подъема уровня провоспалительных цитокинов в моче при обострении хронического калькулезного пиелонефрита // Саратовский научно-медицинский журнал. – 2011. – Т. 7 (прил.). – С. 143. [Glybochko PV, Zakharova NB, Ponukalin AN, et al. Diagnostic value of the increased levels of proinflammatory cytokines in the urine during exacerbation of chronic calculous pyelonephritis. *Saratovskiy nauchno-meditsinskiy zhurnal*. 2011;7(Suppl.):143. (In Russ.)]
8. Захарова Н.Б., Пастушкова Л.Х., Ларина И.М., и др. Значение протеомного состава мочи при заболеваниях мочевыводящих путей (обзор литературы) // Экспериментальная и клиническая урология. – 2017. – № 1. – С. 22–26. [Zakharova NB, Pastushkova LH, Larina IM, et al. The importance of the proteomic composition of urine in urinary tract diseases. Literature review of literature. *Experimental and clinical urology*. 2017;(1):22-26. (In Russ.)]
9. Морозов Д.А., Морозова О.Л., Захарова Н.Б., Лакомова Д.Ю. Патогенетические основы и современные проблемы диагностики хронического обструктивного пиелонефрита у детей // Урология. – 2013. – № 2. – С. 129–134. [Morozov DA, Morozova OL, Zakharova NB, Lakomova DYu. Pathogenetical bases and current problems of diagnosis of chronic obstructive pyelonephritis in children. *Urologiia*. 2013;(2):129-134. (In Russ.)]
10. Алексеев А.В., Гильманов А.Ж., Гатиятуллина Р.С., Ракипов И.Г. Современные биомаркеры острого повреждения почек // Практическая медицина. – 2014. – № 3. – С. 22–27. [Alekseev AV, Gilmanov AZh, Gatiyatullina RS, Rakipov IG. Recent biomarkers of acute renal injury. *Prakticheskaja medicina*. 2014;(3):22-27. (In Russ.)]
11. Кореньков Д.Г., Марусанов В.Е., Мишина Т.П., Павлов А.Л. Провоспалительные цитокины в определении степени активности хронического пиелонефрита // Урологические ведомости. – 2015. – Т. 5. – № 4. – С. 13–19. [Korenkov DG, Marusanov VE, Mishina TP, Pavlov AL Proinflammatory cytokines in determining the degree of activity of chronic pyelonephritis. *Urologicheskie vedomosti*. 2015;5(4):13-19. (In Russ.)]
12. Добронравов В.А. Обзор патофизиологии острого повреждения почек // Смирнов А.В., Добронравов В.А., Румянцев А.Ш. Острое повреждение почек. – М.: МИА, 2015. – С. 30–79. [Dobronravov VA. Overview of the pathophysiology of acute kidney injury. In: Smirnov AV, Dobronravov VA, Rumyantsev AS. Acute kidney injury. Moscow: MIA; 2015. P. 30-79. (In Russ.)]
13. Damman K, Masson S, Hillege HL, et al. Tubular damage and worsening renal function in chronic heart failure. *JACC Heart Fail*. 2013;1(5):417-424. doi: 10.1016/j.jchf.2013.05.007.
14. Крайдашенко О.В., Долинная М.А. Роль биомаркеров в оценке характера повреждений почек у больных гипертонической болезнью // Клиническая нефрология. – 2014. – № 3. – С. 23–25. [Kraydashenko OV, Dolinnaya MA. Biomarkers in assessment of renal involvement in patients with arterial hypertension. *Klinicheskaja nefrologija*. 2014;(3):23-25. (In Russ.)]
15. Dendooven A, Ishola DA Jr, Nguyen TQ, et al. Oxidative stress in obstructive nephropathy. *Int J Exp Path*. 2010;92(3):202-210. doi: 10.1111/j.1365-2613.2010.00730.x.
16. Семикина Е.Л., Русаков А.А., Филянская Е.Г., и др. Уровень факторов ангиогенеза в моче при одностороннем гидронефрозе у детей раннего возраста — различия концентрации

in situ и в мочевом пузыре // Медицинская иммунология. – 2015. – Т. 17, специальный выпуск. – С. 210–211. [Semikina EL, Rusakov AA, Filyanskaya EG, et al. Uroven faktorov angiogeneza v moche pri odnostoronnem gidronefroze u detej rannego vozrasta – razlichija koncentracii *in situ* i v mochevom puzyre. *Medicinskaja immunologija*. 2015;17(special issue):210-211. (In Russ.)]

17. Shiomi A, Usui T. Pivotal Roles of GM-CSF in Autoimmunity and Inflammation. *Mediators Inflamm*. 2015;2015:1-13. doi: 10.1155/2015/568543.

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