

Effect of Metformine (Glucophage) on Renal Function after Complete Unilateral Ureteral Obstruction in Dog

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Abstract: Urethral obstruction is not regarded only as an operational and anatomical case but also as a complicated issue of molecular and biological cascade resulted of obstruction which is imposed on renal tissue. Upper part obstruction of urethra is one of the most important urological issues. The aim of this study was to determine the effect of Metformine (Glucophage) on renal function after complete unilateral urethral obstruction in dog. In the present study 24 adult native dogs (20-30 kg) were used for this study. These animals were fed with standard feeds and Water was provided *ad libitum*. Dogs were divided into 4 groups: group 1(n=6), pseudo abdominal cavity operation, group 2: UUU (Unilateral Ureteral Obstruction): For 14 consecutive days ureter was obstructed (n=6), group 3: UUU+ Metformine (1500mg/every Dog): After Unilateral Ureteral Obstruction for 14 consecutive day's metformine was administrated (n=6), group 4: UUU + Vit E (800IU/Dog): After Unilateral Ureteral Obstruction for 14 consecutive day's Vit E was administrated (n=6). In the present study it was clear that Metformine has a meaningful anti inflammatory effect on renal tissue compared with vitamin E as well as an efficient role in renal function improvement especially in terms of cyto-protection when artery ischemia and ureter obstruction nonetheless the drug has had a degenerative effect on canine renal tissue.

Key words: Metformine • Unilateral Ureteral Obstruction • Dog • Renal

INTRODUCTION

Today's, urethra obstruction is not regarded only as an operational and anatomical case but also as a complicated issue of molecular and biological cascade resulted of obstruction which is imposed on renal tissue. Upper part obstruction of urethra is one of the most important urological issues. Molecular and cellular events caused by obstruction will lead to damage renal function, permanently and progressively [1]. Obstructive nephropathy leads to permanent and progressive changes in renal function as well as fibrosis of renal tissue. Pathologic changes such as renal fibrosis, renal tubular atrophy, tissue inflammation and renal cell apoptosis [1]. Various factors such as nuclear kappa B factors (TNF- β), beta growth factor (TGF- β), intracellular adhesive molecule (ICAM) and tumor necrotic factor of Alfa (TNF- α) probably involve in some tissue changes caused by this clinical condition [1]. Metformine is an edible drug

which is used to control the blood glucose of second type diabetics. Metformine has useful and various metabolic effects such as anti hypertension, anti hyperlipidemia. Recent studies have demonstrated that the intracellular target of the drug is activated protein kinas with AMP. AMPK acts as an intracellular sensor and creates intracellular energy balance. It has been shown that Metformine and bigvanidal compounds has anti inflammatory effects [2]. Such that as explained by researchers, Metformine can decrease mRNA production in endothelial adhesive proteins like VCAM and ICAM-1 and controlling the TNF- α [3, 4]. Metformine also can decrease IL-6 secretion by means of Alfa tumor necrotic factor. Furthermore, the drug can prevent pre-inflammatory cytokines like IL, IL6, IL8 [2]. Finally, Metformine prevents beta nuclear factor by means of TNF- α which is one of effective inducing inflammatory factors [5,6]. As mentioned before, the aim of the study is evaluating the remedial effects of Metformine as an anti

inflammatory, anti oxidative stress and ulcer rehabilitative on cellular and pathologic changes in renal tissue following unilateral urethral obstruction. Murales *et al.* in 2010 demonstrated that the drug has rehabilitative effects on renal function following nephrotoxicity induced by gentamycin [7]. Kikuo *et al.*, in 2006 conducted a study in which the role of Metformine as controlling factor of pre-inflammatory process and controlling of beta kappa nuclear factor in human intravascular system [8]. In the study conducted by Jatwa in 2010 the effect of Metformine on renal microsomal proteins arising from second type diabetic was evaluated by dexamethasone [5]. In the study conducted by Calvert *et al.*, in 2008 it was demonstrated that the drug can prevents production of beta nuclear factors by means of tumor necrotic factor as well as inflammation induction in endothelial cells [9]. Therefore the aim of this study was to determine the effect of Metformine (Glucophage) on renal function after complete unilateral ureteral obstruction in dog.

MATERIAL AND METHODS

In present study 24 adult native dogs (20-30 kg) were used for these studies. These animals were fed with standard feeds and Water was provided *ad libitum*. Dogs divided into the following groups:

- Gr. 1-Only abdominal cavity opened (Pseudo operated) and without any handling was closed (n=6).
- Gr.2-UUO (Unilateral Ureteral Obstruction): For 14 consecutive days ureter was obstructed (n=6).
- Gr.3-UUO+ Metformine (1500mg/every Dog): After Unilateral Ureteral Obstruction for 14 consecutive day's metformine was administrated (n=6).
- Gr. 4-UUO + Vit E (800IU/Dog): After Unilateral Ureteral Obstruction for 14 consecutive day's Vit E was administrated (n=6).

In this study different anesthetic agents were used as Acepromazine (0.1ml/kg), Ketamine (1ml/kg), Also cephalosporin (30mg/kg) for prevention of infection was used. Unilateral ureteral obstruction by ventral midline celiotomy in left kidney were performed and after 14 days renal samples by this method were taken, the samples were fixed in formalin 10% and transferred to laboratory of pathology in Faculty of Veterinary of Tabriz branch Islamic Azad University and these samples by Masson's trichrome were stained.

RESULTS AND DISCUSSION

In the present study it was clear that Metformine has a meaningful anti-inflammatory effect on renal tissue compared with vitamin E as well as an efficient role in renal function improvement especially in terms of cyto-protection when artery ischemia and ureter obstruction nonetheless the drug has had a degenerative effect on canine renal tissue.

Similar and contradictive results Were reported by other researchers their researchers with our findings are observed [10]. According to Pilmore the drug is the first medicine recommended internationally against diabetes nevertheless its administration for renal patients is limited because of lactic acidosis induction; this condition will be aggravated when coincidental events like hypoxia occur. Also, Pilmore states that although the drug has had prohibited in dialysis patients, the studies have shown that it is effective in chronic kidney deficiency (CKD) and following kidney transplantation for cardiovascular system. Lactic acidosis can have degenerative effects on kidney, heart deficiency and liver diseases. It seems that the main reason of acidosis is the control of glucose production from lactate in liver by Metformine and its accumulation causes to renal damage. On the other hand the occurrence of lactic acidosis leads to hypertension [10].

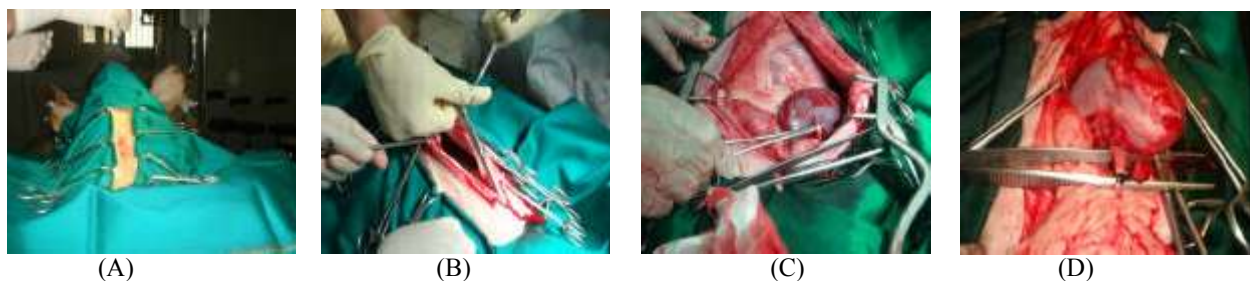


Fig. 1: Surgical stages of Unilateral Ureteral Obstruction (A, B, C, D).

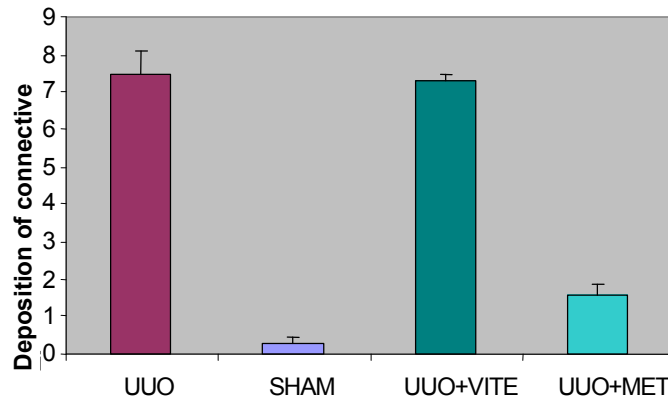


Fig. 1: Mean of deposition of connective tissue changes in renal tissue of control and treatment groups, N=5 (Mean±SEM)

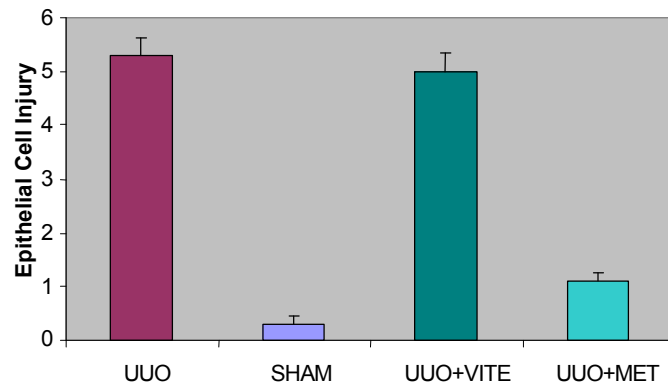


Fig. 2: Mean of epithelial cell injury changes in renal tissue of control and treatment groups, N=5 (Mean±SEM)

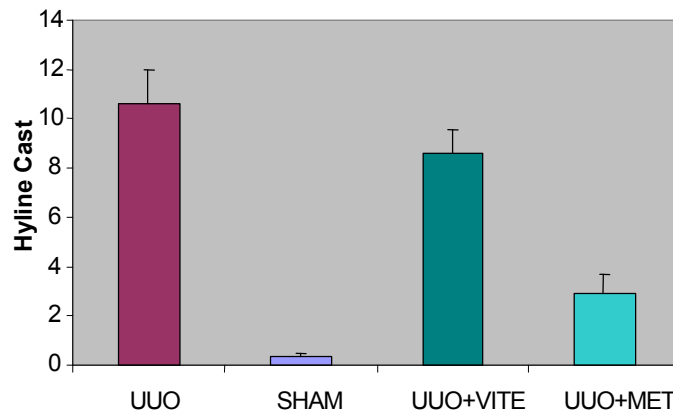


Fig. 3: Mean of hyaline cast changes in renal tissue of control and treatment groups, N=5 (Mean±SEM)

Nye *et al.*, cleared that Metformine besides the blood glucose control has an important role in macrovascular problems because of kidney deficiency [11]. As it was observed from the results, there are contradictive effects of renal function in undertreated animals and humans with Metformine which may be explained by referring to pathobiological effects. With regard to mentioned cases it is revealed that Metformine has bilateral effects on renal

tissue and these effects arise of chronic or acute damages. It seems that in acute damages in which the renal system has not the sufficient time to confront the event, fast lactic acidosis causes damage to renal functional cells. On the other hand, due to hypotension as a result of lactic acidosis, renal damage following Metformine administration increases. In chronic renal damages as well as in long term consumption of the drug

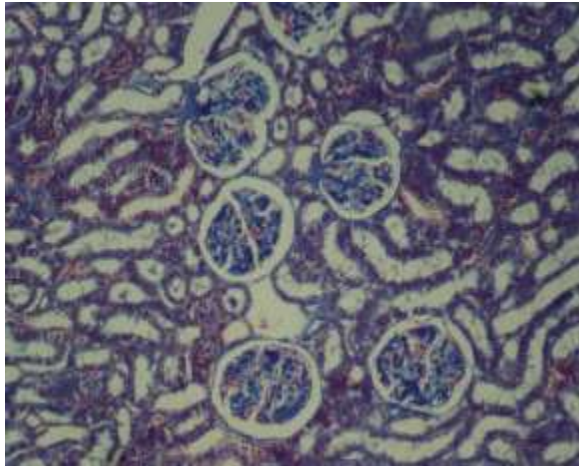


Fig. 4: Microscopic appearance of renal tissue belong to group SHAM (Trichrome masson staining ×40)

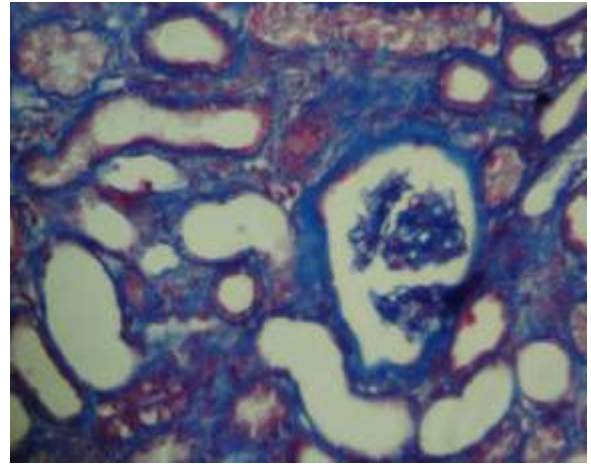


Fig. 6: Microscopic appearance of renal tissue belong to group UUO + Vit E 800IU/Dog (Trichrome masson staining ×40)

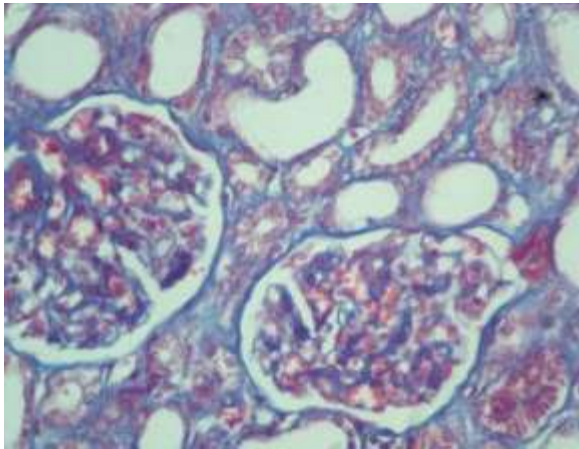


Fig. 5: Microscopic appearance of renal tissue belong to group UUO + Metformine 1500mg/day (Trichrome masson staining ×40)

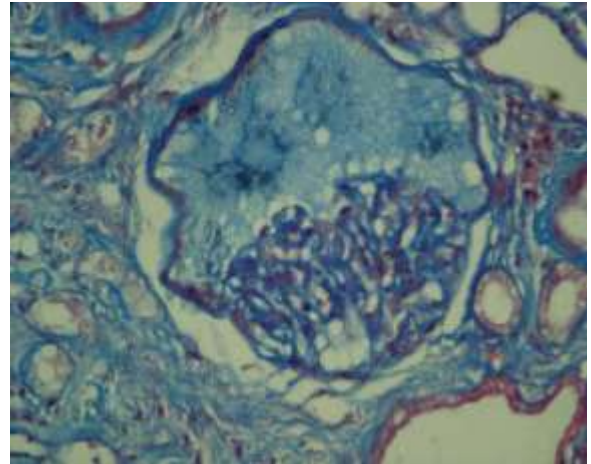


Fig. 7: Microscopic appearance of renal tissue belong to group with UUO (Trichrome masson staining ×40)

Table 1: Mean of Glumerular injury occurrence in different groups

Groups	Mean ± SEM
UUO	4.6 0.3
SHAM	0.3 0.1528
UUO+VIT E	4.6 0.2211
UUO+MET	1.4 0.2211

Table 2: Mean of Epithelial cell injury occurrence in different groups

Groups	Mean ± SEM
UUO	5.3 6.33
SHAM	0.3 0.1528
UUO+VIT E	5.0 0.3333
UUO+MET	1.1 0.1795

Table 3: Mean of deposition of connective tissue occurrence in different groups

Groups	Mean ± SEM
UUO	7.5 0.6191
SHAM	0.3 0.1528
UUO+VIT E	7.3 0.9195
UUO+MET	1.6 0.2667

Table 4: Mean of hyaline cast occurrence in different groups

Groups	Mean ± SEM
UUO	10.6 1.368
SHAM	0.3 0.1528
UUO+VIT E	8.6 0.9568
UUO+MET	2.9 0.7219

the pathophysiologic process is changed and it seems that in chronic damages the drug has more cytoprotective effects. It seems that its vulnerary effects on organs' function especially kidney is the result of the influence of the drug on vascular function by induction of vascular dilation by means of endothelium.

It was cleared in Vitale *et al.*, study that the drug causes to tissue function improvement by induction of improved indexes of coagulation and endothelial activity [12]. Even as mentioned by Alessi *et al.*, the anti-inflammatory effect of the drug is so strong that has anti cancer effects and can cause the suppression of cancerous and inflammatory cells. Furthermore, it has been cleared that the effect of Metformine on macrovascular is such that in under-treatment patients can decrease cardiovascular problems [13]. In the study conducted by Jhonson it was cleared that cardiac MI damages in the patients treated by Metformine has decreased 79% [14]. In any case the results concluded by the present study showed that the drug has meaningful efficient effects on renal function in long term consumption compared with vitamin E and it is recommended that small livestock domestic experts enjoy its anti-inflammatory and cell protective properties in some conditions like nonexistence of previous renal damages especially acute damages.

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