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RESEARCH ARTICLE

Excretory Urography by Subcutaneous Injection of Iodixanol in Persian Squirrel (*Sciurus Anomalous*)

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ABSTRACT

There are many indications for excretory urography in humans and animals. Intravenous urography (IVU) is the most practical method about other urography techniques are used because of difficulties for finding veins in IVU, due to small size of the patients. This study was performed to evaluate the feasibility of subcutaneous injection of iodixanol in providing a safe and diagnostic urogram in Persian squirrel. Twelve clinically healthy adult Persian squirrels were prepared and kept for two weeks prior to study. Blood tests were performed 7 days prior to the study. After eighteen hour fasting, animals were sedated by using xylazine/diazepam cocktail (xylazine 5mg/kg, diazepam 30mg/kg). Lateral and ventrodorsal control radiographs were taken. Thirteen hundred and 1800 mg iodine per kilogram body weight of iodixanol was injected subcutaneously over shoulder area in Persian squirrels (each dose for six Persian squirrels). Lateral and ventrodorsal radiographs were taken every 5 minutes until the pyelogram was finished. Blood tests were performed 5 days after the study. Histopathologic samples were taken from skin, kidneys, ureters and urinary bladder. The kidneys of squirrels were bean-shaped and their size was approximately 1.7×0.8 cm in ventrodorsal view for both kidneys. Subcutaneous injection of iodixanol was successful to show pyelogram, uretrogram and cystogram but it was unsuccessful in showing nephrogram without pyelogram except in one case (8.33%). Good pictures of nephrograms, calices and the ureters were obtained approximately 70 min after injection. There were no abnormal clinical signs after one week of experiment. There were no abnormal blood chemistry and hematological changes. Urinary system and skin microscopic examinations were normal. It is concluded that subcutaneous urography is an effective and reliable method for urography studies in squirrel except for nephrogram. More investigations are needed to study reasons for the lack of nephrogram, it may be due to incomplete preparation.

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INTRODUCTION

Persian Squirrel (*Sciurus anumalus*) is a small rodent which lives in oak forest of the North West and West provinces of Iran. Squirrel is a wild mammal which is kept as a pet since last decade in Iran and therefore the numbers of referred cases to the clinics have been increased.

Radiography is used for diagnosis of abdominal disorders in exotic animals as well as squirrel. Excretory urography is used for morphological and functional studies of the urinary tracts in man and animals (Thrall, 2007). Excretory urography has not been reported in squirrel at the present knowledge of authors.

There are many routes for delivering contrast media to the patient for excretory urography i.e. intravenous, intraosseous (Saglam *et al.,* 2004), intramuscular (Knotek *et al.,* 2004), intracardiac (Hubmann, 1980) and subcutaneous (Cerny *et al.,* 1967). Intravenous urography (IVU) is the most practical method. It is desirable in urinary tract contrast study to have a secure route for administration of contrast media, having a very safe contrast material which does not have any bad side effect, to have short and restricted timing for showing different

part of urinary system. Despite improvement in techniques and equipment for obtaining venous access, in small mammals, it is not always possible to achieve a secure IV line. For this reason an alternative route for contrast media administration is desirable in these animals (Porzio *et al*., 2001). Therefore subcutaneous urography may be feasible to be achieved in squirrel due to inaccessible vein route. The aim of this study was to evaluate the efficacy of subcutaneous injection of iodixanol (a non-ionic iodinated contrast agent under the trade name Visipaque) in providing a safe and diagnostic urogram in Persian squirrel.

MATERIALS AND METHODS

Twelve clinically healthy adult Persian squirrels, with no evidence of any urinary system disorder were prepared from animal selling center and kept for two weeks prior to study. Blood tests were performed 7 days prior to the study and no abnormality in hematological and bio-chemical factors was detected (Khazraiinia *et al.*, 2008).

Before administration of contrast media the squirrels were fasted for 18 hours, and 20 mg per kilogram body weight of dimethicone was given orally 2 hours before starting the procedure. To facilitate handling the animals and to get good-quality radiographs, the animals were sedated with xylazine/diazepam cocktail (xylazine 5mg/kg, diazepam 30mg/kg) administered intramuscularly.

Control lateral (L) and ventrodorsal (VD) radiographs were taken prior to contrast study with focus-film distance (FFD) of 100 cm and Kilovolt peak (kVP): of 45-47, Milliampere per seconds (mAs: 2.0) using a portable Sedcal X-Ray machine (Fig. 1 and Fig. 2). But unfortunately no cleansing of the large bowel was successful even after 18 hours of fasting in eleven cases.

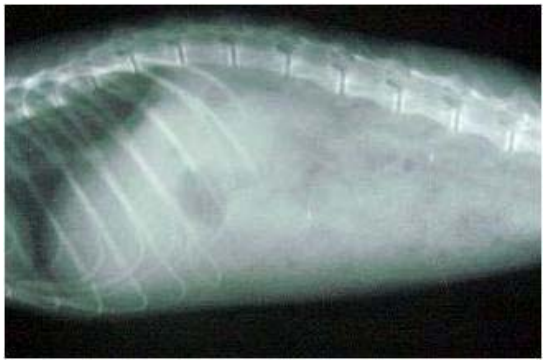

Fig. 1: Lateral view of control radiograph.

Thirteen hundreds and 1800 mg of iodine/kg b. wt (iodixanol; Visipaque©) were injected subcutaneously over shoulder joint (each dose for six Persian squirrels). Eighteen hindered mg was tried to find out any complication associated with using higher doses of non ionized Iodine as contrast media (Agut *et al.*, 1999; Ajadi *et al*., 2006).

Lateral and VD radiographs were taken after every 5 minutes until the pyelogram was finished. All animals were kept for one week after experiment to note any abnormality in animals. Blood tests were performed 5 days after the study. Then squirrels were euthanized by over dose of anesthetic drug and with permission from Iranian Society for the Prevention of Cruelty to Animal. Pathologic samples of kidneys and the skin were taken and sent by routine manner for microscopic examinations. Data was analyzed statistically using student t-test.

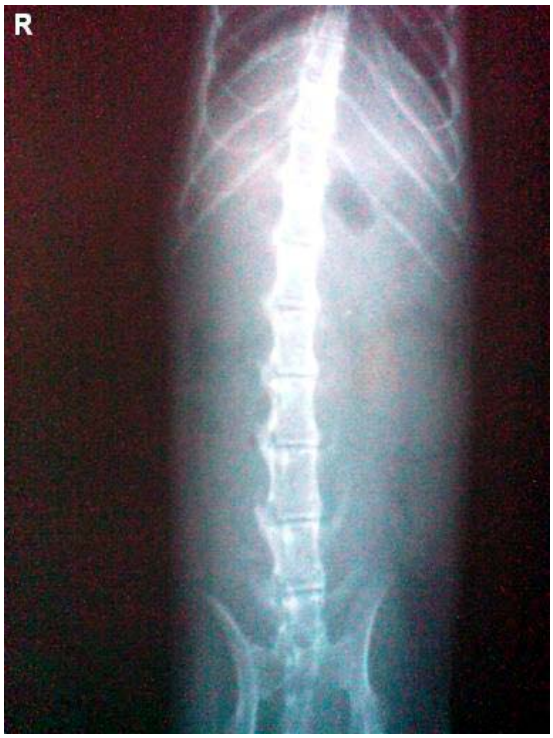

Fig. 2: Ventrodorsal view of control radiograph.

RESULTS

The shape of the kidneys of squirrels were bean shaped, their sizes were approximately 1.7×0.8 cm for both kidneys in gross anatomic investigation. Right kidney was slightly cranial than left. Right kidneys were seen at the level of first to third lumbar vertebrae and left kidneys were seen at the level of third to fifth lumbar vertebrae in VD views. The squirrel's kidneys were approximately 2.14±0.09 times the length of the second lumbar vertebral body in VD view (Fig. 3 and Fig. 4).

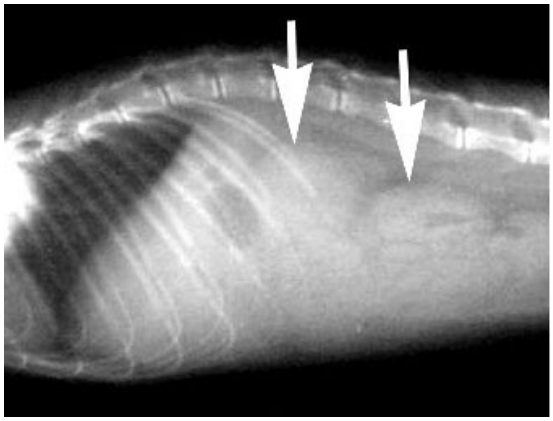

Fig. 3: Lateral view radiograph of nephrogram phase. Arrow: nephrogram phase.

Increased opacity of the kidneys (nephrogram) was seen only in one case of 1300 mg dosage group, starting at 15min, having the optimum opacity at 20min and lasted until 230min. Nephrogram was seen clearly in both L and VD views in this only case. No nephrogram without pyelogram was detected in other 11 cases at all (Fig. 3 and Fig. 4).

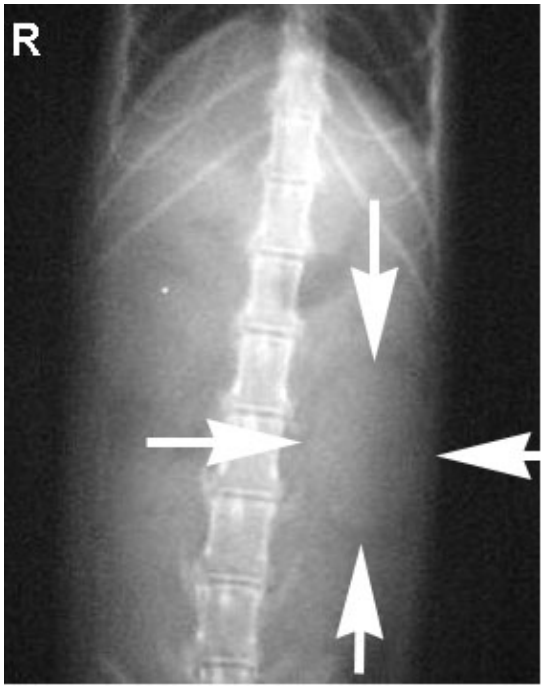

Fig. 4: Ventrodorsal view radiograph of nephrogram phase. Arrow: nephrogram phase.

In 1300 mg dosage group and in L view, starting of pyelogram was 32.50±8.2min and optimum visualization was between 45.00±10.60 to 225.00±5.00min (Table 1). For VD view, pyelogram started at 44.16±12.41min and optimum visualization was between 54.00±13.87 to 228.33±3.89min (Fig. 5 and Fig. 6).

In 1800 mg dosage and in L views, starting of pyelogram was 26.66±9.30min and optimum visualization was between 41.66±15.38 to 223.75±6.07min (Table 1). For VD views, pyelogram started at 38.33±10.32min and optimum visualization was between 48.75±15.47 to 224.58±5.82min (Fig. 5 and Fig. 6). No fading was detected for nephrogram up to 223.13±5.43min. It started at this time when subcutaneously injected contrast media was completely vanished.

Ureters were seen in only L views in all cases (100%) of 1300 and 1800mg group at the time of 55.00±4.47 and 52.00±10.80min and optimum visualization at the time of 60.00±6.32 to 216.66±5.16min and 57.00±7.50 to 231.33 ±5.16min, respectively (Table 2). In 1300mg group, ureters were only seen in one case in VD views at the time of 60 minutes and optimum visualization at the time of 70 to 220 minuets (Fig. 7) whereas ureters were not seen in all VD views in 1800mg group.

Bladder was seen in both views at the time of 22.5±4.18 to 22.83±2.04min in group 1300 mg and 1800 mg respectively and lasted up to 240 minuets. Bladder was extended up to the level of fifth lumbar vertebrae. The bladder wall was clearly defined from its surroundings (Fig. 5 and Fig. 6).

There were no abnormal clinical signs after one week of experiment. There were no abnormal biochemical and hemtological changes. Urinary system and skin histopathological examinations were normal.

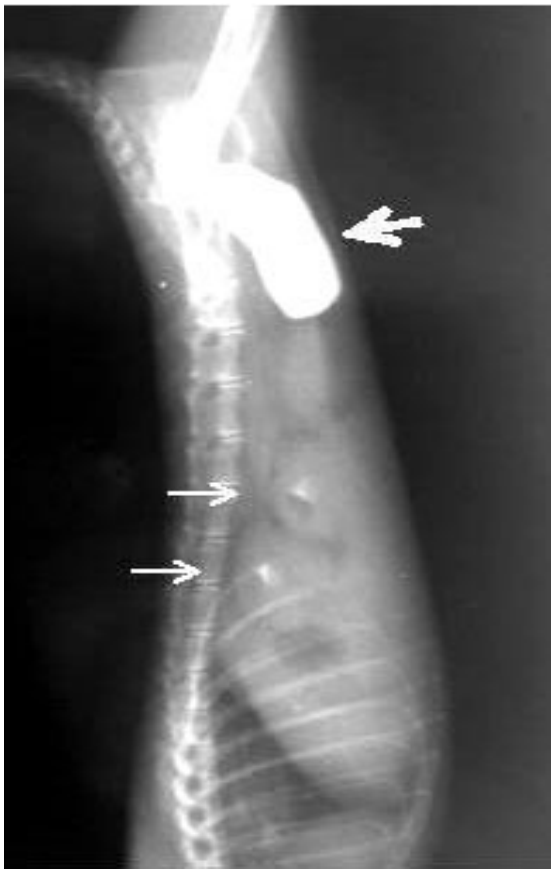

Fig. 5: Lateral view radiograph of pyelogram and cystogram phases. Small arrow: pyelogram phase and large arrow: distended urinary bladder.

DISCUSSION

Squirrel is a wild mammal which is not kept usually as a pet around the world. It became very popular to keep squirrel as a pet during the last decade in Iran. Radiography is used to diagnose abnormalities like other species in squirrel. Normal anatomy of some parts of this animal is reported (Thorington and Darrow, 2000) and radiographic diagnosis of its disorders like nutritional secondary hyperparathyroidism and ricketts was reported (Vajhi *et al.*, 2006).

Plain radiography of the abdomen may show kidneys in high quality radiographs and with animal preparations. Unlike other animals like cat and rabbits, in squirrel even full bladder is not visible on plain radiographs. Urinary system can be investigated by means of urography (Heuter, 2005), ultrasonography (Mayor *et al*., 1995), nuclear medicine (Daniel *et al*., 1999) and MRI (Klein and Pollack, 1992; Nikken and Krestin, 2007).

Urography is used by injection of contrast media via intravenous, subcutaneous, intramuscular, intracardiac and

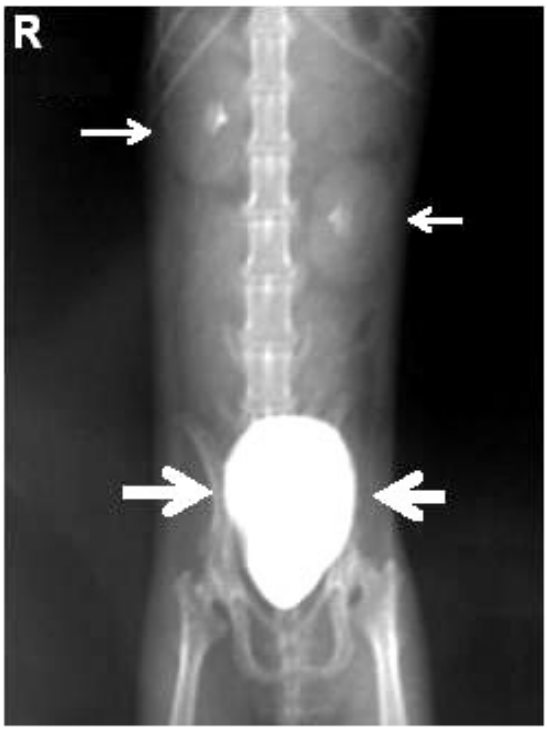

Fig. 6: Ventrodorsal view radiograph of pyelogram and cystogram phases. Small arrow: pyelogram phase and large arrow: distended urinary bladder.

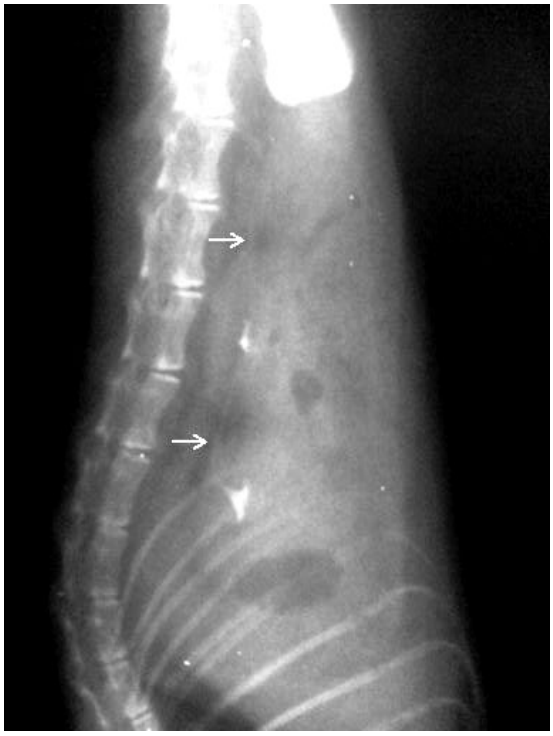

Fig. 7: Lateral view radiograph of uretrogram phase. Arrow: ureters.

intraosseous routes in animals (Hubmann, 1980; Porzio *et al*., 2001; Knotek *et al*., 2004; Saglam *et al*., 2004) and human (Cerny *et al*., 1967; Ngo *et al*., 2009). Intravenous urography is the most commonly used procedure for making urography, but in very small sized animals and neonates, it is difficult to find veins for injection of iodine contrast materials (Porzio *et al*., 2001; Saglam *et al*., 2004). Intraosseous injection is used for patients that it is difficult to have access to their veins (Ngo *et al*., 2009) and it is also used for injection of contrast media for procedures like urography (Saglam *et al*., 2004). The quality of radiographs is very good in intraoseous urography and the timing for these procedures is very short and takes about 15 minutes to complete the whole procedures (Saglam *et al*., 2004). But this technique is very invasive and osteochonderosis (22.7% cases) was reported as a complication of interaosseous urography (Porzio *et al*., 2001). Subcutaneous and intramuscular injection for urography is reported in humans and also in small sized animals where other routes for injection are not very easy so it seems that these routes are feasible in small sized animals like squirrel.

Subcutaneous urography was reported in human many years ago (Cerny *et al*., 1967) but there is no report of this procedure in animals and humans in recent years.

Different kinds of contrast media have been used for excretory urography (Newhouse *et al*., 1994; Chuang *et al*., 2009). Some articles confirmed that the iodine dosage is more important than iodine concentration in excretory urography (Crespi-Porro *et al*., 1991). Iodixanol showed no significant metabolism in humans and had an excellent renal safety (McCullough, 2006; Reed *et al*., 2009).

Intraosseous, intramuscular, intravenous, and also subcutaneous urography is not reported in squirrel at the present knowledge of authors. Subcutaneous urographgy using iodixanol was used to study the efficacy of this technique to show normal passage of contrast media in squirrel in this study.

Eight hundred mg of iodine per kilogram body weight up to 1000 mg is reported to be adequate to delineate urinary systems in human and dog and cat (Kealy and McAllister, 2000). This amount of iodixanol was unable to delineate nephrogram, pyelogram for a very long time in squirrel (Tavana *et al*., 2008). That is why 1300 and 1800 mg iodine/kg BW in the form of iodixanol was tried. This amount was able to show the urinary system completely.

There was no significant difference for nephrogram delineation between 1300 and 1800 mg iodine/kg BW. Both doses were unable to show nephrogram without pyelogram very clearly in all cases except in one case of 1300mg group. Many different factors like off feeding, water withholding and emptying large intestine were considered as causes for not showing the nephrogram alone (Kealy and McAllister, 2000). It should be emphasized that even after many attempts, there was failure to empty large intestine and this was true when control radiographs were examined before contrast studies. It is concluded that failure to empty large bowels properly is the actual reason for not delineating nephrogram. The only case in which nephrogram was shown very clearly in both L and VD radiographs the large intestine was completely empty. It is important to find out practical ways to empty large intestine completely and easily before applying subcutaneous or other routes for urography in squirrel.

Table 1: Comparison of pyelogram in I and II groups in lateral and ventrodorsal view

Group	Phase	Number	Mean min.	SD min.	Minimum min.	Maximum min.	P value
Lateral view							
I	Starting of	6	32.50	8.21	25.00	40.00	0.13
II	pyelogram	6	26.66	9.30	15.00	35.00	
I	Optimum view of	6	45.50	10.60	35.00	60.00	0.48
II	pyelogram	6	41.66	15.38	30.00	60.00	
I	Finishing of	6	225.00	5.00	220.00	230.00	0.74
II	pyelogram	6	223.75	6.07	220.00	230.00	
Ventrodorsal view							
I	Starting of	6	44.16	12.41	25.00	50.00	0.29
II	pyelogram	6	38.33	10.32	30.00	60.00	
I	Optimum view of	6	54.00	13.87	35.00	70.00	0.66
II	pyelogram	6	48.75	15.47	35.00	80.00	
I	Finishing of	6	228.33	3.89	210.00	220.00	0.77
II	pyelogram	6	224.58	5.82	205.00	220.00	

Table 2: Comparison of uretrogram in I and II groups in lateral view

Group	Phase	Number	Mean min.	SD min.	Minimum min.	Maximum min.	P value
I	Starting of	6	55.00	4.47	50.00	60.00	0.75
II	uretrogram	6	52.00	10.80	40.00	70.00	
I	Optimum view of	6	60.00	6.32	50.00	65.00	0.54
II	uretrogram	6	57.00	7.50	50.00	70.00	
I	Finishing of	6	216.66	5.16	210.00	220.00	0.17
II	uretrogram	6	231.33	5.16	210.00	220.00	

Pyelogram was shown very clearly and for a very long period of times in both positionings and both doses of 1300 and 1800 mg of iodine/kg BW. There was no significant difference between two doses to show pyelogram, except the time of showing pyelogram was slightly shorter in 1800 than in 1300mg of iodine/kg BW, but this time difference was not significant (Table 1). So the best dose for urography was suggested 1300mg of iodine per kilogram body weight in squirrel. Subcutaneous urography was very capable to show pyelogram from 20min up to 230min and this long range of time gives clinician to take radiographs without having stress for losing critical best time for urograms. This critical time is very short for IVU and intraosseous urography which is between 2 to 15min (Saglam *et al*., 2004).

Uretrogram was seen best in L view in all cases of both groups in this study where VD view was able to show uretrogram in only one case of 1300mg of iodine per kilogram body weight group. It was interesting that uretrogrms were shown in entire length of ureters unlike the ureters of cat and dogs that is shown in peristaltic waves (Kealy and McAllister, 2000). There was no significant difference between two doses to show uretrogram, except the time of showing uretrogram was slightly shorter in 1800 than 1300mg of iodine per kilogram body weight, but this time difference was not significant (Table 2). Uretrogram was shown from 60 to 230min very clearly. For showing entire length of ureters "unlike IVU in cats and dogs" in this study it is concluded that it can be due to two reasons, first due to slow and gradual release of contrast media from subcutaneous tissues, second with "less probability" due to histological differences of ureters of squirrel to cats and dogs. It is suggested that histological studies of the ureters of squirrel should be done. Cystogram was shown very clearly like IVU in cats and dogs at the end of study from 25 to 240min. The amount of contrast media was increased in the bladder by increasing the time and complete distended bladder can be seen from 90 to 240min if voiding not happened. Voiding was happened in 5 cases so best time for detecting distended bladder was at least 145min. Bladder was seen as a pear shaped structure in both views in front of pelvic rim and its wall from its contents could be seen clearly. There was no significant abnormality in histological examinations of kidneys, ureters, bladder and site of injection in subcutaneous region due to both doses of contrast materials.

Nephrogram without pyelogram was seen in one squirrel and pyelogram, cystogram and uretrogram were being investigated during a long period of times. It is also reported that base on ionizing or non-ionizing component of the contrast media like visipaque, there was no complication when this drug is used for IVU in human. It is reported that when non-anesthetized person or animals were injected with contrast media some complications like nausea, abdominal pain, discomfort, vomiting, anaphylactic shock, collapse and death were happened (Katayama *et al.*, 1990). There were no such complications during procedures and no illnesses were seen up to two weeks afterward in this study.

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