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Experimental renal artery embolization with iohexol-ethanol and barium-ethanol in dogs

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Abstract : The present study was performed to investigate the effect of iohexol-ethanol mixture and barium-ethanol mixture on the induction of transcatheter renal artery embolization in healthy 18 dogs, which were divided into two groups of 9 dogs and the 9 dogs were divided into 3 subgroups of 3 dogs. The renal artery embolization was undertaken unilaterally with the dose of 1.5, 2.0, and 3.0 ml/kg iohexol-ethanol mixture and with the dose of 0.2, 0.4, and 0.8 m*l*/kg barium-ethanol mixture. And serum chemistry on 0, 1, 3, 7, and 14 days, intravenous pyelography on 7 days, angiography on 14 days, and histopathology on 14 days were evaluated. Serum BUN and creatinine concentration of two groups with iohexol-ethanol mixture and barium-ethanol mixture administration were mildly increased at 1 day after injection of embolic materials and then returned to baseline. No significant changes in BUN and creatinine levels occurred in any of dogs. In all dogs with the dose of 1.5 m*l*/kg iohexol-ethanol mixture, the renal arteries were not embolized. All dogs with the dose of 3.0 m*l*/kg died. In all dogs with the dose of 2.0 m*l*/kg, the treated arteries were completely occluded. In barium-ethanol mixture administered group, the renal artery in one dog with the dose of 0.2 m*l*/kg was not embolized. In all dogs with the dose of 0.8 m*l*/kg, the renal arteries were completely embolized, but local overembolization occured in two dogs. All animals with the dose of 0.4 m*l*/kg had effective embolization and no evidence of radiopaque barium opacity in systemic arteries distal to the renal artery was found. All embolized kidneys were shrunk and decreased in size in gross examination and were shown diffuse necrosis in histopathologic examination. In the present study, renal arteries were embolized with the dose of 2.0 m*l*/kg iohexol-ethanol mixture or 0.4 m*l*/kg barium-ethanol mixture. And it is considered that the dose had a satisfactory embolic effect.

Key words : transcatheter renal artery embolization, ethanol, iohexol, barium, dog

Introduction

Interventional radiology is to manipulate catheters and needles and to use other instruments such as radiologic imaging modalities for guidance. It is used most often in the management of the trauma patient to control hemorrhage and drain fluid collections[1]. Since transcatheter embolization was first described as a kind of interventional radiology for the treatment of renal carcinoma, selective renal artery embolization using a wide variety of agents has been embolized successfully in both man and experimental animals to control various renal neoplasms, either preoperatively to facilitate nephrectomy or palliative therapy in advanced cases[2]. And as an alternative to surgery, the patient was managed with transcatheter embolization[3,4,5]. In these efforts to avoid partial or total nephrectomy, catheter embolization of the arteriovenous fistula was also attempted[3,4]. Iatrogenic renovascular injury is a distinct from a trauma owing to the large number of percutaneous nephrostomies, percutaneous nephrolithotomies and percutaneous renal biopsies being performed. Needle injury of a branch of the renal artery may result in the formation of a pseudo-aneurysm or an arteriovenous fistula. Transarterial embolization is an

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established primary mode of therapy for these types of injuries. Embolization, being less invasive than surgery, has a high success rate and can be repeated if necessary[6,7]. Transcatheter arterial embolization and occlusion techniques are becoming accepted in the management of selected cases of renal cell carcinoma, vascular renal tumor and poorly differentiated adenocarcinoma with pure ethanol in patients[8].

A variety of embolic materials including muscle, fat, fascia, plain catgut[9], gelfoam, gelfoam and steel coil, barium suspension[10], poly (vinyl acetate) emulsion[11], cellulose porous beads[12], hot contrast medium[13], sodium tetradecyl sulfate[14], autologous clot[9,15], pure ethanol, Gianturco coils and polyvinyl alcohol foam powder with gelatin sponge[16] have been used. Subcutaneous fat was then obtained from the thigh and injected through the catheter[4]. In another report, one cubic centimeter of autologous blood clot was injected[3].

Pure ethanol within embolic materials has been used as a vascular occluding agent both clinically and experimentally[2]. And pure ethanol causes permanent embolism as well as tissue damage[17].

Barium was the most efficient in producing diffuse infarcts within gelfoam and steel coil. All kidneys showed a diffuse and uniform decrease in size and infarcts were complete[10].

The previous studies were mainly about individual use of ethanol and barium sulfate and the authors could hardly find articles concerning ethanol and barium mixture as an embolic material. The present study was performed to apply the transcatheter renal artery embolization into veterinary medicine. And the purpose of this study was to investigate the effect of transcatheter renal artery embolization with iohexol-ethanol mixture and barium-ethanol mixture and to determine the optimal dose of each embolic material in dogs.

Materials and Methods

Experimental animals

Eighteen mature, clinically healthy, mongrel dogs of both sexes with weight ranging from 2 to 5 kg were used. The 18 dogs were divided into two groups of 9 dogs and the 9 dogs were divided into 3 subgroups of 3 dogs according to a dose per kg and transcatheter renal artery embolization was performed.

The embolic materials with iohexol-ehanol mixture and barium-ethanol mixture were used individually in each group. The embolization was undertaken in unilaterally renal artery with the dose of 1.5 m*l*/kg, 2.0 m*l*/kg, and 3.0 m*l*/kg iohexol-ethanol mixture and with the dose of 0.2 m*l*/kg, 0.4 m*l*/kg, 0.8 m*l*/kg barium-ethanol mixture.

Preparation of embolic materials

In iohexol-ethanol mixture, 300 mg iodine iohexol (Omnipaque® 300 mg I/m*l*, Nycomed Ireland LTD., Cork, Ireland) and pure ethanol (Absolute Alcohol A. R. quality, Hayman Limited, England) were mixed with the same dose. The solution consisted of 50% ethanol by volume and contained 150 mg iodine per ml iohexol.

In barium-ethanol mixture, barium suspension (Solotop® sol. 120, Taejoon co., particle size 1 μm) were prepared by mixing 3 m*l* of pure ethanol with 1 m*l* of barium sulfate. The solution consisted of 33% ethanol by volume.

Embolization Technique

The dogs were anesthetized with thiopental sodium (15 mg/kg, IV, penthotal sodium®, Joongwei, Korea), and maintained with isoflurane (Aerane®, ilsung Co., Korea). Before the procedure, for the prophylactic use, broad-spectrum antibiotics ampicillin (20 mg/kg, Penbrex®, Sam Yang Co., Korea) or enrofloxacin (5 mg/kg, Baytril®, Bayer Korea Co., Korea) were given intravenously.

Skin and subcutaneous tissues were incised until femoral artery was exposed. And then catheter (Fastraker-18®, Cook, U. S. A.) and guide wire was placed into the femoral artery with cut-down, and inserted into the unilateral renal artery. Pre-operative angiography was performed for choosing the best vessels for selective renal artery embolization. Catheter was advanced into abdominal aorta through the femoral artery and then introduced selective renal artery under fluoroscopy. And the prepared embolic materials were injected into the renal artery. The kidney was perfused with heparinized saline for 2 minutes before and after injection of embolic materials. Post-operative angiography was performed to confirm embolization of the renal artery.

Serum Chemistry

Blood samples were collected on 0, 1, 3, 7, and 14 days after iohexol-ethanol mixture and barium-ethanol mixture administration and BUN and creatinine levels were measured.

Intravenous pyelography & Angiography

Intravenous pyelography was performed via cephalic

vein with bolus injection on 7 days after embolization. Iohexol was used with the dose of 800 mg iodine per body weight. Radiographs were obtained immediately and 5, 10, 20, and 40 minutes after injection of contrast medium. And then intravenous pyelographic findings were analyzed and compared with each subgroup.

Angiography was also performed on 14 days after transcatheter renal artery embolization. Under fluoroscopy, catheter was selectively inserted into the treated renal artery. About 3 m*l* of iohexol was injected during renal angiography.

Histopathology

Tissue samples from embolic and nonembolic kidneys were examined histopathologically on 14 days after embolization in all dogs.

Both kidneys with their attached pedicles, the aorta, vena cava, and the lungs (barium dogs only) were removed for gross examinations. Microscopic examination focused on the extent of the renal infarcts.

Results

Serum Chemistry

BUN and creatinine were measured on 0, 1, 3, 7, and 14 days after transcatheter renal artery embolization. The mean BUN and creatinine of each treated group were shown in Fig 1 and 2. Serum BUN and creatinine concentrations of each group were mildly increased on 1 day, but the levels declined and then returned to baseline and no significant changes in BUN and creatinine levels occurred in any of dogs.

Intravenous pyelography and angiography

Intravenous pyelography was performed on 7 days after embolization. In dogs treated with iohexol-ethanol mixture, kidneys and ureters were identified except 3 dogs with 2.0 m*l*/kg dose (Table 1, Fig 3).

In one dog treated with the dose of 0.2 m*l*/kg barium-ethanol mixture, the renal artery was not completely

Table 1. Identified kidney and ureter by intravenous pyelography in dogs treated with iohexol-ethanol mixture

Dose (m*l*/kg)	No.	Nephrogram (n)	Ureterogram (n)
1.5	3	3	3
2.0	3	0	0
3.0*	3	-	-

* : Deceased 3 dogs

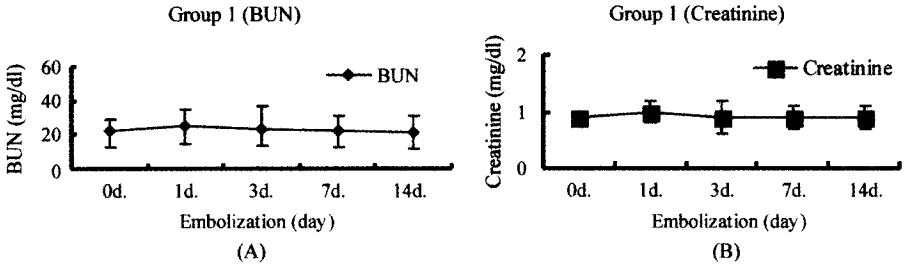

Fig 1. BUN (A) and creatinine (B) levels in dogs treated with iohexol-ethanol mixture on 0, 1, 3, 7, and 14 days after embolization (Mean± SD).

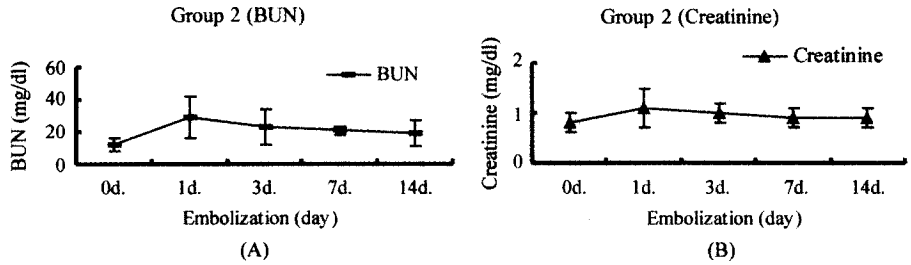

Fig 2. BUN (A) and creatinine (B) in dogs treated with barium-ethanol mixture on 0, 1, 3, 7, and 14 days after embolization (Mean± SD).

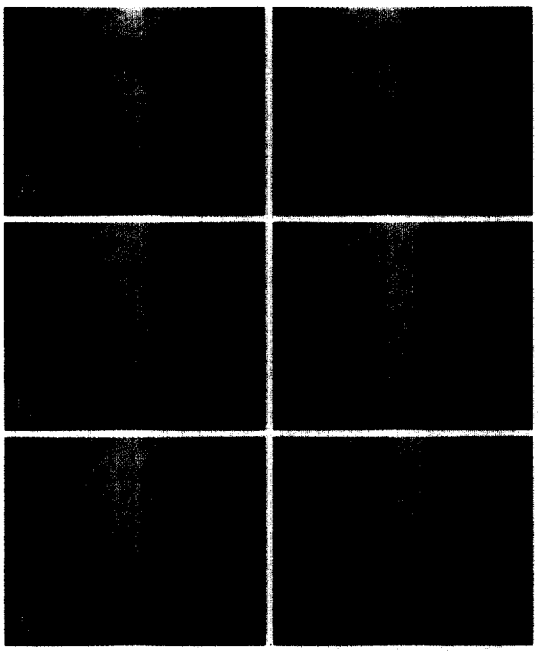

Fig 3. Intravenous pyelography with the dose of 2.0 ml/kg iohexol-ethanol mixture in a dog on 7 days. A: before, B: 0, C: 5, D: 10, E: 20, and F: 40 minutes after contrast medium administration.

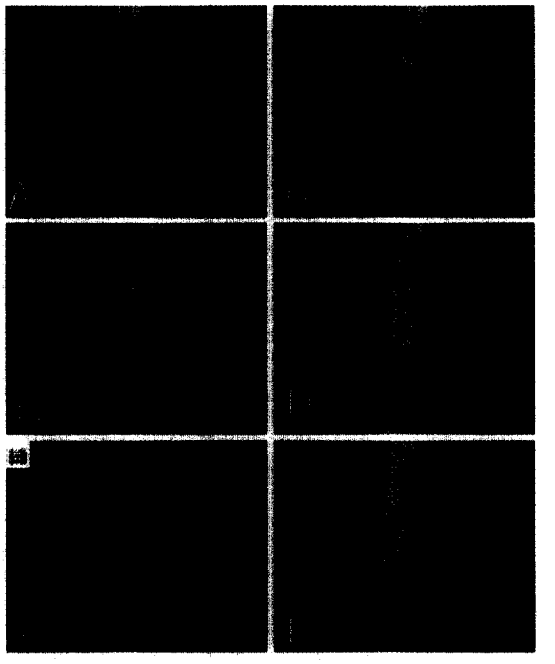

Fig 4. Intravenous pyelography with the dose of 0.4 ml/kg barium-ethanol mixture in a dog on 7 days. A: before, B: 0, C: 5, D: 10, E: 20, and F: 40 minutes after contrast medium administration.

embolized. The kidney and ureter was opacified. Kidneys and ureters of all dogs were not identified with the dose of 0.4 ml/kg and 0.8 ml/kg. With the dose of 0.8 ml/kg, embolization was complete, but local overembolization occurred in two dogs. Radiopaque barium opacity adjacent to kidney was identified due to regurgitation of embolic materials on survey radiographs. In all dogs with the dose of 0.4 ml/kg, renal arteries were completely embolized. And no evidence of radiopaque barium opacity in systemic arteries distal to the renal artery was also found (Table 2, Fig 4).

Angiography was performed on 14 days after procedure. The result of angiography was the same that of intravenous pyelography. In dogs treated with iohexol-ethanol mixture, 2.0 ml/kg dose could be embolized, and in dogs treated with barium-ethanol mixture, more than 0.4 ml/kg dose could. In group of barium-ethanol mixture administration, barium in the renal vascular trees became more dense after embolization and the kidney became smaller on 14 days. There was no excretion of contrast medium in any embolized kidney with barium-ethanol mixture.

Table 2. Identified kidney and ureter by intravenous pyelography in dogs treated with barium-ethanol mixture

Dose (ml/kg)	No.	Nephrogram (n)	Ureterogram (n)
0.2	3	1	1
0.4	3	0	0
0.8#	3	0	0

#: Contrast agent regurgitation in 2 dogs

Histopathology

All animals were sacrificed on 14 days after embolization. There was good correlation between the radiographic demonstration of occlusion and the presence of emboli on histological examination.

On 14 days, all embolized kidneys were shrinked and decreased in size on gross examination (Fig 5). All embolized kidneys treated with iohexol-ethanol mixture had cortical infarction and complete necrosis of the renal parenchyma. All kidneys except one dog treated with 0.2 ml/kg barium-ethanol mixture, uniformly decreased in size and showed complete infarcts. Barium was found in glomerular capillaries and interstitial spaces of both

Fig 5. Gross findings of kidneys with the dose of 2.0 m*l*/kg iohexol-ethanol mixture (A) and 0.4 m*l*/kg barium-ethanol mixture (B) on 14 days. Embolized kidneys were decreased in size and shrunk.

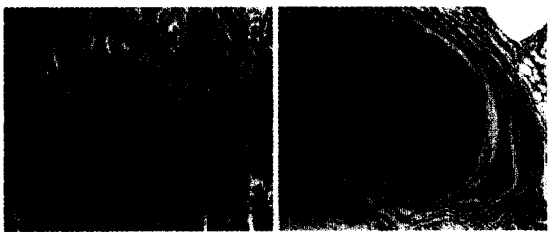

Fig 6. Diffuse renal necrosis with the dose of 2.0 m*l*/kg iohexol-ethanol mixture (A) and renal artery thrombosis with the dose of 0.4 m*l*/kg barium-ethanol mixture (B) in the histopathologic findings on 14 days.

cortex and medulla. There was also a granulomatous reaction around the barium.

Discussion

In human patients, transcatheter arterial embolization has proved to be a satisfactory alternative to surgery for the control of bleeding from various organs. And it is easily performed, causes minimal discomfort to the patient, and serious complications are rare[7]. A variety of embolic materials were used for the transcatheter renal artery embolization. Ellman *et al*[18]. reported that the autologous clot, gelfoam, Ivalon®, steel coils, and several polymers were limited by inability to produce complete infarction, usually leaving at least a rim of viable tissue fed by capsular vessels. Some of polymers were difficult to administer. Total ablation of renal parenchyma could not be achieved with gelfoam and gelfoam-plus-coil embolization. Recanalization of coil thrombi might be led to induction of renal ischemia and subsequent abnormal production of renin[10]. Ethanol and barium were used for the transcatheter renal artery embolization in the present study. Ethanol has been used clinically to ablate kidneys because of several highly desirable features. Ethanol is readily available, inexpensive, easy to administer, and create complete renal infarction. In laboratory animals and clinical studies, no damage has occurred outside of the target organ[19]. And barium was the most efficient in producing diffuse infarcts[10].

Multiple mechanisms of action of intra-arterial ethanol are proposed, including perivascular tissue toxicity, sludging of erythrocytes in small arteries, small artery spasm, and endothelial damage[8]. Pure ethanol is a liquid embolic material that causes permanent vascular occlusion and is used widely for interventional procedures such as renal ablation or percutaneous ethanol injection therapy for tumor[8,20,21].

The immediate embolic effect is greater in the pure ethanol than the iohexol-ethanol. However, a major disadvantage of this agent is its radiolucency, making it difficult to inject. To opacify ethanol is used to contrast medium such as metrizamide, iodized oil, and iohexol[22]. Therefore iohexol and barium contrast medium were tested to opacify ethanol in our experimental study. Ellman *et al*[18]. stated that an ethanol concentration below 30% did not produce renal damage. Park *et al*[23]. reported that dogs which received 50% ethanol showed little or no change in the renal parenchyma. Miyazano *et al*[22]. proved 66% ethanol produces an equal embolic effect on renal parenchyma to that of pure ethanol. In the present, it was proved that 50% ethanol produce embolic effect on renal parenchyma. These radiopaque embolic materials may be attributed to cessation of blood flow under fluoroscopy.

Barium suspension (Micropaque®, particle size 0.5-1.5 μm) was prepared by thoroughly mixing 2 m*l* of heparinized saline with 1 m*l* of barium sulfate[10]. In this paper, barium suspension (Solotop® sol. 120, particle size 1 μm) was prepared by mixing 1, 2, 3, or 4 m*l* of pure ethanol with 1 m*l* of barium sulfate individually. In mixing 1 or 2 m*l* of pure ethanol with 1 m*l* of barium sulfate, the solutions were too thick to inject through the catheter. In mixing 4 m*l* of ethanol with 1 m*l* barium sulfate, the solution was not seen under fluoroscopy.

Thus, in barium-ethanol mixture administered group, embolic materials were prepared with mixture of 3.0 m*l* ethanol and 1 m*l* barium.

A variety of doses in transcatheter renal artery embolization was reported. In the pure ethanol, a dose of 1 m*l* per 4 pounds body weight is usually adequate. The dose of up to 1 m*l* per 2 pounds body weight can be safely tolerated in humans[8]. Pure ethanol with 0.3 m*l* per kg injection of renal artery were reported in rabbit kidneys[2] and 0.22 m*l* per kg (1 m*l*/10 lb body weight) in dog kidneys[18,24]. The agent was also infused into the selective renal artery of dogs with 0.3 m*l*/kg[22]. But, in this investigation ethanol was injected 2.0 m*l*/kg in dog kidneys. The embolized dose was four times that of the reported in humans. Barium suspension filled the entire renal artery system with the dose of 3-4 m*l* in 15-30 kg dogs. In the present study barium-ethanol mixture filled with the dose of 0.4-1.6 m*l* in 2-4 kg dogs.

After procedure serum BUN and creatinine were evaluated. On 1 day after injection, serum BUN and creatinine concentration of two groups were mildly increased in a contrast-induced nephropathy. The levels declined and then returned to baseline. Bechtel *et al*[25]. were published no significant changes in BUN and creatinine levels in any of dogs.

In intravenous pyelography and angiography, contrast medium was not shown in the embolized kidneys and ureters. The renal arteries were embolized completely with the dose of 2.0 m*l*/kg iohexol-ethanol mixture and 0.4 m*l*/kg barium-ethanol mixture. In this investigation manipulations were performed under fluoroscopy to prevent reflux of the embolic materials. However, over-embolization occurred in some dogs due to injection of the excessive embolic materials. To prevent problems with reflux, balloon catheters have been employed, but are relatively expensive[18].

Conclusively, the dose of 2.0 m*l*/kg iohexol-ethanol mixture and 0.4 m*l*/kg barium-ethanol mixture caused complete embolization and no evidences of side effects were shown. In group 2, embolic effect was enhanced with barium sulfate in addition to the effect of pure ethanol, which was thought to be due to the synergy effect of diffuse necrosis by barium sulfate and permanent occlusion by pure ethanol.

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개에서 iohexol-ethanol 및 barium-ethanol을 이용한 실험적 신동맥 색전술

황국진 · 장동우 · 서민호 · 정주현 · 최민철 · 윤정희

서울대학교 수의과대학 방사선과학교실

(2001년 8월 28일 게재승인)

국문초록 : 임상적으로 건강한 18두의 개에서 선택적인 삽관술을 통해 ethanol과 iohexol 합제 혹은 ethanol과 barium 합제를 이용한 신동맥 색전술을 실시하였다. Iohexol과 ethanol 합제는 1.5, 2.0 및 3.0 m*l*/kg을 적용하였고 barium과 ethanol 합제는 0.2, 0.4 및 0.8 m*l*/kg을 각각 적용하였다. 검사항목으로 신기능 이상 유무의 판단 척도로서 혈청 BUN과 creatinine을 술전 및 술후 경시적으로 측정하였으며, 배설성 요로조영술을 7일째, 혈관조영술 및 조직병리학적 검사를 14일째 각각 실시하였다. 혈청 BUN 수치와 creatinine 수치는 시술 후 1일째 조영제 주입에 따른 일시적 변화로 다소 상승하였으나 전반적으로 정상 범주에 속하였다. 배설성 요로조영술 및 혈관조영술 결과 iohexol과 ethanol 합제를 사용한 1군에서는 1.5 m*l*/kg 용량으로 색전되지 않아 시술한 신장이 영상화되었으며 3.0 m*l*/kg 투여에서는 용량이 과도하여 실험동물이 폐사하였으나 2.0 m*l*/kg에서는 모두 색전되었다. barium과 ethanol 합제를 사용한 2군에서는 0.2 m*l*/kg 1두는 색전되지 않아 신장 및 요관이 영상화되었으며 0.8 m*l*/kg 2두는 용량 과다로 신장 주위에 X-선 비투과성 barium 음영이 확인되었다. 그 중 0.4 m*l*/kg 3두 모두는 색전되어 신장 및 요관이 영상화되지 않았으며 색전 물질이 역류되지 않아 신장 주위에 X-선 비투과성 barium 음영도 확인되지 않았다. 색전술을 실시하고 2주 후에 신장을 적출하여 육안적으로 관찰한 결과 1군과 2군 모두 색전된 신장의 크기는 반대쪽에 비해 그 크기가 감소하였다. 이상의 결과로 iohexol과 ethanol 합제를 사용한 1군에서는 2.0 m*l*/kg이 barium과 ethanol 합제를 사용한 2군에서는 0.4 m*l*/kg이 가장 적절하였다. 모든 개는 그 용량에서 만족스런 색전 효과를 나타내었다.

핵심어 : 카테터를 이용한 신동맥색전술, 에탄올, iohexol, barium, 개