Development of a mouse model of contrast agent-induced acute kidney injury

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BACKGROUND

Contrast-induced acute kidney injury (CI-AKI) is a side effects of iodine containing radiocontrast agents (CA) used in emergency and elective settings. CI-AKI is diagnosed if serum creatinine (sCr) increases by either 0.5 mg/dL or 25% within 48 hours after CA administration[1]. SCr levels usually rise within 24 hours after contrast administration, peak within 3-5 days and return to baseline in 10-14 days. In worst cases acute renal failure may develop with oligouria (<400 mL urine/day) that eventually require temporary hemodialysis. The incidence is 6.4% based on a meta analysis[2], but it can be as high as 50% in patients with multiple risk factors[3]. Chronic kidney disease is the most important risk factor of CI-AKI, and patients with increased BUN or plasma creatinine at the time of CA administration are also at high risk. Other important risk factors are diabetes mellitus, sepsis, hypotension, dehydration, cardiovascular disease, use of diuretics, advanced age (>70 years) and hypertension[4]. Hydration is the only generally accepted and proved preventive therapy of CI-AKI[4]. The mechanism of CI-AKI is complex and far from being fully understood. However, the consensus is that CA-induced vasoconstriction especially in the renal medulla is one of the main causes leading to CI-AKI.

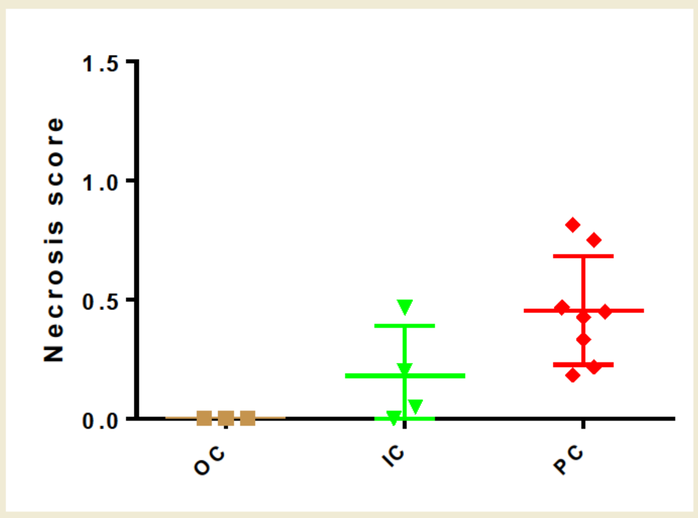
1. Clin Kidney J 5:102-108, 2012; 2. Eur J Radiol 81:2554-2561, 2012; 3. J Intervent Cardiol 23:78-85, 2010; 4. Curr Probl Diagn Radiol 44:501-4, 2015

AIM

Ischemia is an important contributor of CI-AKI pathomechanism, therefore, our aim was to developed and characterize model of transient renal ischemia-reperfusion combined with contras agent administration to study the pathomechanism and therapeutic options in CI-AKI in mice.

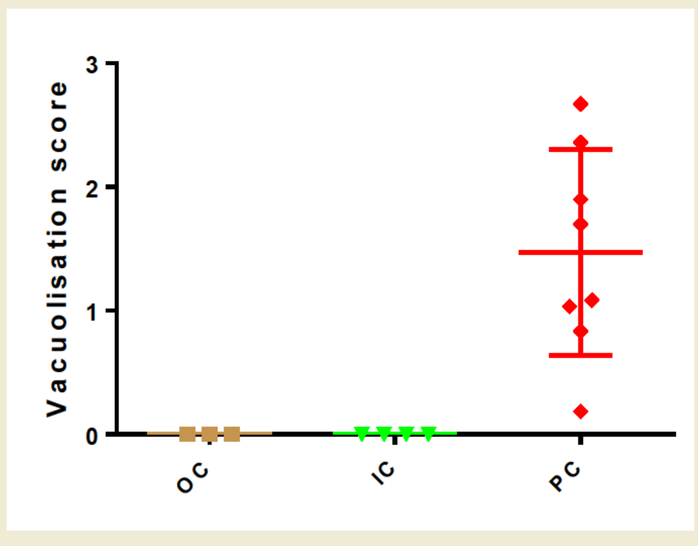
RESULTS

Tubular necrosis score at day 1



Ischemia alone caused some degree of tubular necrosis which was increased by administration of omnipaque to mice with ischemic kidneys.

Tubular vacuolation at day 1



Treatment with omnipaque or ischemia alone caused no vacuolation but administration of omnipaque to mice with ischemic kidneys caused strong tubular vacuolation.

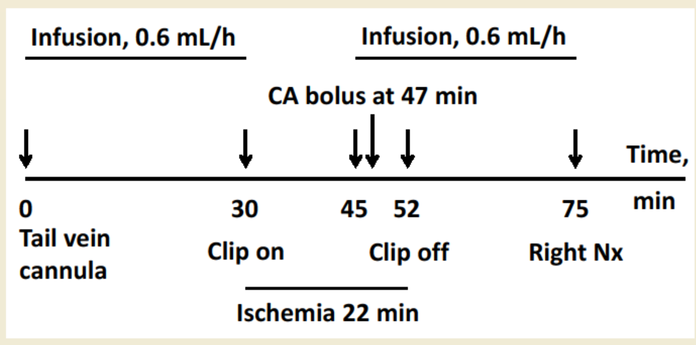
MATERIALS AND METHODS

The renal pedicle was clamped for 22 min in male NMRI mice (n=7-12/group), and iohexol (IO, 8 mg/kg, 350 mg/mL) was administered i.v. 5 min before reperfusion in the positive control group (PC). The intervention groups were treated with 0.6 mL physiological saline (hydration, H) or theophylline (Th, 30 mg/kg) added to the hydration regimen. The result were compared to an ischemic control group (IC) not treated with IO, and an IO group without ischemia (OC). The right kidney was removed in all groups.

Assay of urea, creatinin and NGAL

NGAL levels were evaluated with mouse Lipocalin-2/NGAL DuoSet ELISA Development kit (R&D Systems, USA), as described by the manufacturer. Serum and urine creatinine levels, and serum urea levels were evaluated with colorimetric assays (Diagnosticum Ltd, Budapest, Hungary) according to the manufacturer's protocol.

Timeline of the experiment



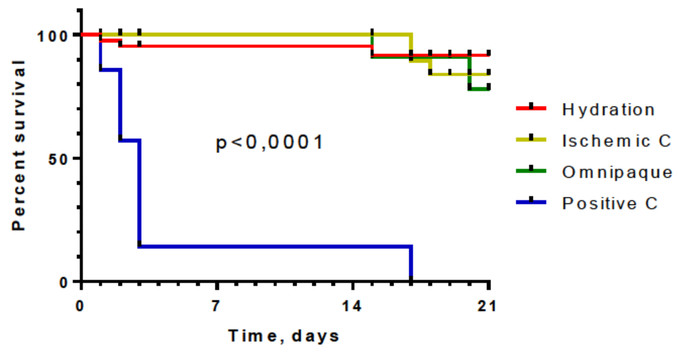
Experimental series

Serie 1: Survival
- Groups: Omnipaque (OC, no I/R)
- I/R – Ischemic control (IC)
- I/R + O – Positive control (PC)
- I/R + O + hydration (saline) – (Hydration)

Serie 2: Harvest at day 1
- Groups: Negative control (NC) – No I/R, no CA)
- Omnipaque (OC, no I/R)
- I/R – Ischemic control (IC)
- I/R + O – Positive control (PC)
- I/R + O + hydration (saline) – (Hydration)
- I/R + O + Theophyilline (saline) (Theophyilline)

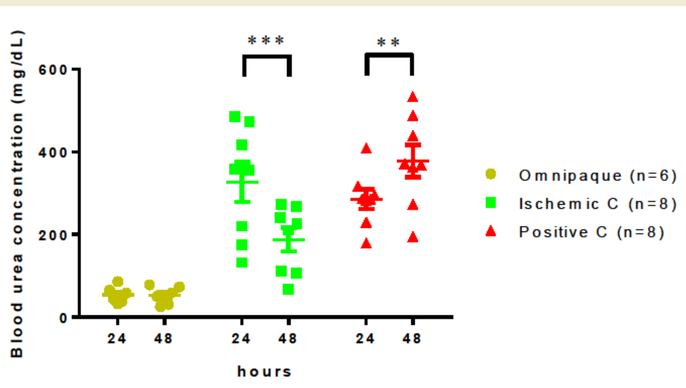
Serie 3: Harvest at day 2
- Groups: Omnipaque (OC, no I/R)
- I/R – Ischemic control (IC)
- I/R + O – Positive control (PC)

Survival of mice in the various groups (n=7-11)



Mice survived up to the end of the 21-day observation period in the IC and NC groups. On the other hand, IO decreased survival to 2-3 days (p<0.001), in the PC group, while hydration restored survival (p<0.001).

Plasma urea concentrations at days 1 and 2



Plasma urea concentration was markedly and similarly elevated in the ischemic control and positive control groups at day 1, but plasma urea levels decreased in the ischemic control group and increased in the positive control group by day 2.

ABSTRACT

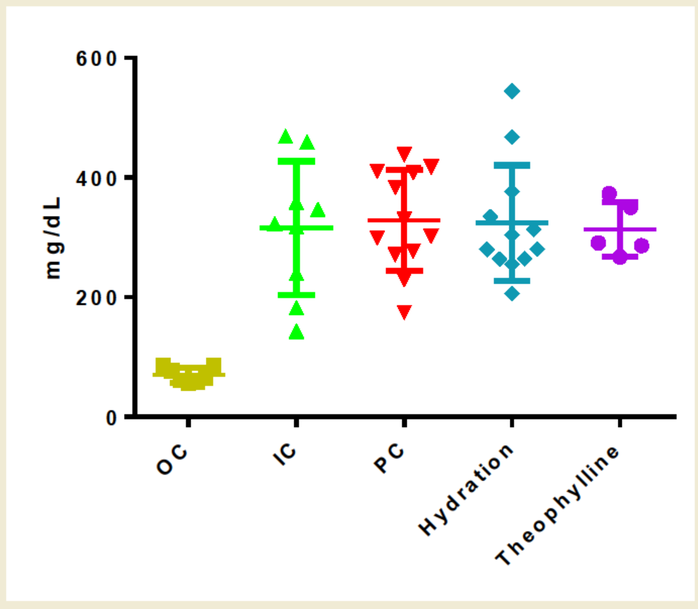
INTRODUCTION AND AIMS: Iodine-containing contrast agents induced acute kidney injury (CI-AKI) can occur in up to 50% of patients in the presence of renal risk factors. Ischemia is an important contributor of CI-AKI pathomechanism, thus we used developed a model of transient renal ischemia-reperfusion in mice to study the pathomechanism and therapeutic options in CI-AKI.

METHODS: The renal pedicle was clamped for 22 min in male NMRI mice (n=7-12/group), and iohexol (IO, 8 mg/kg, 350 mg/mL) was administered i.v. 5 min before reperfusion in the positive control group (PC). The intervention groups were treated with 0.6 mL physiological saline (hydration, H) or theophylline (Th, 30 mg/kg) added to the hydration regimen. The result were compared to an ischemic control group (IC) not treated with IO, and an IO group without ischemia (NC). The right kidney was removed in all groups. The levels of plasma urea, as well as plasma and urinary neutrophil gelatinase-associated lipocalin (NGAL) were measured 24 and 48 hours after ischemia. The kidney was investigated histologically. Survival was studied in a separate cohort.

RESULTS: Mice survived up to the end of the 17-day observation period in the IC and NC groups. On the other hand, IO decreased survival to 2-3 days (p<0.001), in the PC group, while hydration restored survival (p<0.001). Plasma urea concentration was markedly and similarly elevated in all ischemic groups at day 1, while plasma urea levels decreased in the IC group but increased in the PC group. Urinary NGAL excretion corrected for plasma NGAL level (U/P NGAL), a sensitive marker of kidney injury, was considerably elevated already at day 1 in the PC group (29.7±6.3 mg/mg) but it was significantly lower in the IC group (6.1±1.4 mg/mg) and both intervention groups (H: 11.6±2.9; Th: 5.0±1.6 mg/mg; p<0.01 all).

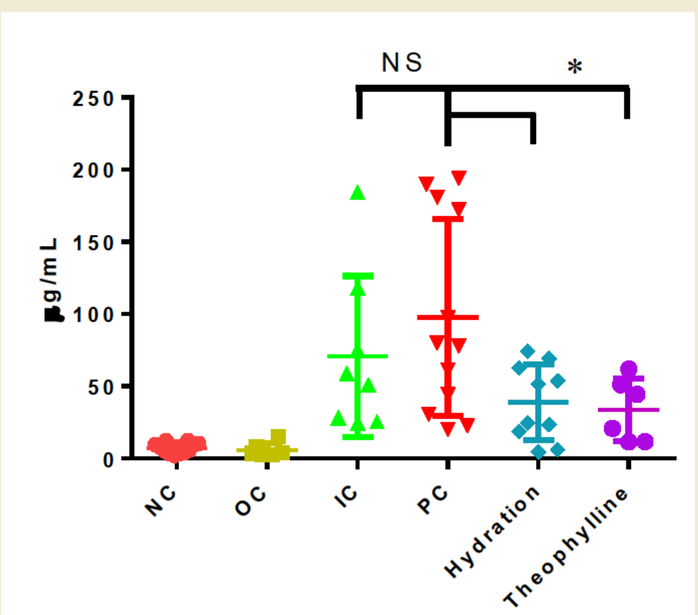
CONCLUSIONS: These results demonstrated that combination of ischemia with contrast agent administration increased renal tubular injury compared to renal ischemia alone. Both hydration and treatment with theophylline proved to be beneficial to prevent CI-AKI.

Plasma urea concentrations at day 1



Hydration and treatment with theophylline did not decrease plasma urea concentration at day 1.

Normalized urine NGAL excretion at day 1



Urinary NGAL excretion was similarly elevated in the ischemic control and positive control groups at day 1, and both hydration and treatment with theophylline decreased urinary NGAL excretion .

CONCLUSIONS:

These results demonstrated that combination of ischemia with contrast agent administration increased renal tubular injury compared to renal ischemia alone. Both hydration and treatment with theophylline proved to be beneficial to prevent CI-AKI.

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