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NEPHROLOGY - ORIGINAL PAPER

Is it possible to prevent contrast-induced nephropathy with dexpanthenol?

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Abstract

Purpose Contrast-induced nephropathy (CIN) is one of the side effects of diagnostic procedures. Oxidative stress plays an important role in CIN's pathophysiology. Dexpanthenol (Dexp) is a substance with antioxidant efficacy. We investigated the likely protective effects of dexpanthenol for CIN.

Methods Twenty-four Sprague–Dawley rats were divided randomly into four groups of 6 rats; control (group 1), Dexp (group 2), CIN (group 3) and Dexp + CIN (group 4). All rats were restricted of water moderately to facilitate of nephrotoxicity. Dexp was administered into the intraperitoneally at a dose of 500 mg/kg for 5 days in groups 2 and 4. The same amount of saline was applied via intraperitoneally to group 1 and 3. In CIN and Dexp + CIN groups, L-NAME (10 mg/kg), tenoxicam (0.5 mg/kg) and sodium amidotrizoate (10 ml/kg) were administered on the 4th day via the tail vein for CIN. All rats were euthanized on the 6th day and samples for biochemical and pathological evaluations were collected.

Results When the Dexp + CIN group and the CIN group were compared, it was found to be provide a significant decline at the level of acute tubular injury and necrosis in kidney biopsies by dexp. Furthermore Dexp significantly reduced the serum cystatin C (Cys-C) levels, not serum creatinine. There was no statistically significant difference between the groups in total oxidant and antioxidant levels.

Conclusions Dexpanthenol did not have significant effect on oxidative stress of acute kidney injury on this rat model. However, it has ameliorated serum Cys-C levels and histopathological findings of CIN.

Keywords Radiocontrast media · Nephrotoxicity · Dexpanthenol · Cystatin C · Apoptosis

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Introduction

Developing technology has led to an increasing number of iodinated contrast studies namely angiography, computerized tomography (CT) for diagnostic and therapeutic purposes. This explains the rising the frequency of CIN in and out patients. Several risk factors have been suggested for the development of CIN, including age (> 75 years), low systolic blood pressure, low hematocrit levels, the amount of contrast agent given and the presence of concomitant diseases (chronic kidney disease, multiple myeloma, etc.) [1].

The risk of CIN in the general population is reported to be around 1–2% and can reach up to 50% in the high-risk population such as those with diabetes mellitus and pre-existing renal impairment [2]. Although CIN is usually reversible and has a low frequency in the normal risk population, it is the third common cause of acute kidney injury in admitted patients [2, 3]. Renal damage by the contrast via increased levels of endothelin, adenosine and reactive oxygen radicals and decreased levels of prostaglandins and nitric oxide have all been accused in pathophysiology [4, 5]. Therefore, an abundant number of studies regarding role of antioxidants in prevention of CIN have been performed [6]. To date most promising antioxidant has been N-acetylcysteine (NAC) which clinically offers a modest if any benefit. The standard of care in preventing CIN; intravenous saline infusions has been challenged lately both due to inefficacy or non-superiority over oral hydration antioxidant [6]. There is still no molecule that is shown to inhibit contrast nephropathy. The search is still continuing to find a suitable agent to prevent contrast nephropathy.

Dexpanthenol (Dexp) or provitamin B5 changes into pantothenic acid (PA) in rat and mammalian tissues when administered orally or parenterally. PA acts by increasing glutathione, acetyl CoA and ATP synthesis [7]. Glutathione and glutathione-dependent peroxidase compose important defense mechanisms for cells against oxidative stress and lipid peroxidation [8]. There are several reports that PA reduces ischemia–reperfusion injury in heart [9], kidney [7], ovarian [10] and brain [11]. Those studies show that the main mechanism of this effect is Dexp's ability to reduce level of malondialdehyde (MDA) in tissues that is the main trigger of oxidative damage pathway leading to lipid peroxidation.

Several antioxidant molecules have been examined for the prevention of CIN but no specific treatment algorithm could be developed due to the inconsistent data [12]. KDIGO guidelines suggest use of isotonic saline with or without bicarbonate and oral NAC [13]. In this rat study, we aimed to investigate effectiveness of Dexp in preventing CIN. To our knowledge, this is the first ever study on Dexp and CIN.

Materials and methods

Sprague–Dawley male rats weighing 250–300 g, 12 weeks old, were recruited in the study. The rats were kept at standard room temperatures (21 ± 2 °C), humidity and lightings were same between groups. All rats received equal amount of liquid and nutrients. The local ethical committee for experimental animal studies approved the study.

A total of 24 rats were divided into four groups as controls (group 1), Dexp (group 2), contrast induced nephropathy (group 3) and Dexp plus contrast induced nephropathy (group 4). Dexp was applied during 5 days at a dose of 500 mg/kg/day (Bepanthene® ampul 500 mg/2 ml) intraperitoneally (i.p) to group 2 and group 4. Control group received only saline (i.p) at the same amount of Dexp for 5 days. All rats were restricted for only water during first 3 days of study period. As described previously in literature, water restriction was performed by allowing the rats to reach the water ad libitum only twice in a day (15 min twice each day) [14]. Water restriction was terminated in all rats on the 4th day of experiment.

Study protocol is demonstrated in Fig. 1.

CIN protocol

This protocol was applied to rats of group 3 and group 4 on the 4th day. To facilitate the formation of CIN, the nitric oxide synthase inhibitor *N*-nitro-L-arginine methyl ester (L-NAME, 10 mg/kg; Sigma-Aldrich) and a cyclooxygenase inhibitor, tenoxicam (0.5 mg/kg; Oksamen-L®) were injected intravenously with 15-min interval before the contrast medium implementation. Following L-NAME and tenoxicam injections, sodium amidotrizoate (Urografin® 10 ml/kg), high osmolar contrast medium, was administered through the tail vein. This procedure was modified from the model that had been defined by others [15, 16].

Euthanasia was performed on day 6. All rats were anesthetized via intramuscular ketamine + xylazine injection under the guidance of specialist veterinarian. Blood samples were collected through cardiac puncture. BUN, creatinine, cystatin-C (Cys-C), and C-reactive protein levels were analyzed with supernatants after serum samples were centrifuged at 3000 rpm for 10 min.

Blood urea nitrogen (BUN) and creatinine levels were analyzed using Beckman Coulter auto-analyzer, and C- reactive protein (CRP) was evaluated by nephelometry (Siemens BN II System) at our central laboratories. Cys-C, glutathione peroxidase (GPx) and superoxide dismutase (SOD) parameters were measured using commercially available ELISA kits (Shanghai Sunred Biological Technology) according to the manufacturer's protocol. Total antioxidant status (TAS) and total oxidant status (TOS) were analyzed using colorimetric

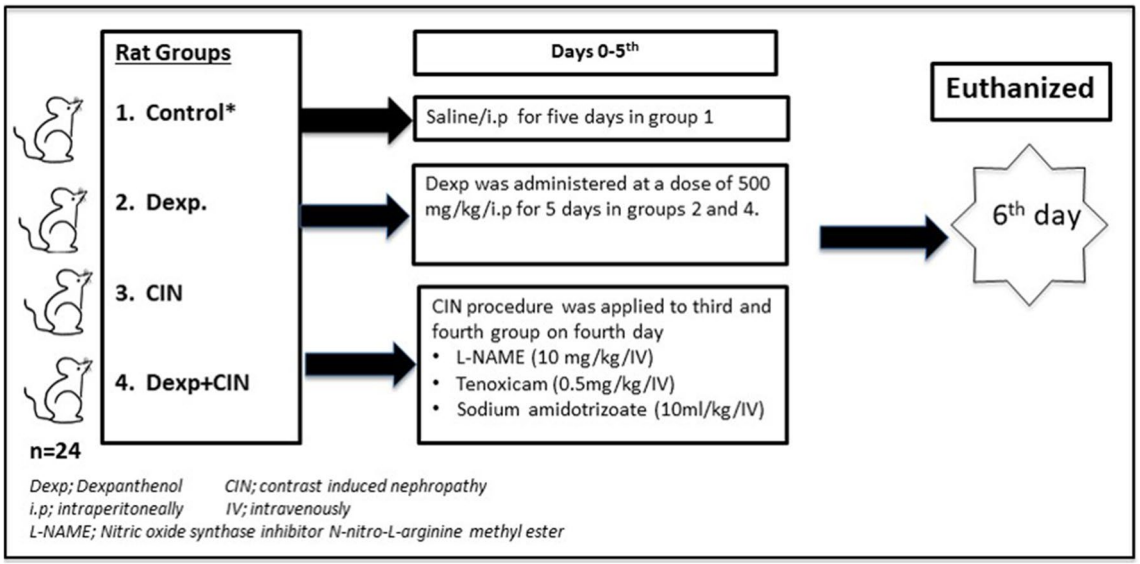

Fig. 1 Study protocol

kits (Rel Assay Diagnostics). The results of TAS and TOS were calculated as mmol Trolox equivalent/L (mmol/L) and μmol H_2O_2 equivalent/L (μmol/L), respectively. Malondialdehyde (MDA), which is an indicator of lipid peroxidation, was assessed as thiobarbituric acid reactive substances (TBARS), using previously described method [17].

Nephrectomy specimens of rats were fixed in 10% buffered formaldehyde for 24 h. Following routine tissue processing, paraffin embedded tissue blocks were sliced into 4-micron sections. H&E stained sections were examined under light microscope for the presence of following features; (a) interstitial capillary congestion, (b) interstitial inflammation, (c) tubular injury including early and late features and tubular dilatation. The localization of capillary congestion, as medullary/cortical/mixed medullary and cortical was noted. The degree of medullary congestion semi quantitatively graded as absent or insignificant (score 0: congestion recognizable under 400× magnification), mild (score 1: congestion recognizable under 200× magnification), moderate (score 2: congestion recognizable under 100× magnification) and severe (score 3: congestion recognizable under 40× magnification). Tubular necrosis, cytoplasmic swelling, tubular dilatation and interstitial inflammation were all semi quantitatively scored as follows; 0: absent, 1: mild, < 25% of the renal parenchyma affected, 2: moderate, 26–50% of the renal parenchyma affected, 3: severe, > 50% of the renal parenchyma affected.

Apoptosis (DNA fragmentation) was detected on paraffin embedded tissue sections by use of the TUNEL (terminal deoxyribonucleotidyl transferase-mediated dUTP-digoxigenin nick-end labeling) assay method (Apoptag reagent, Q-Biogene, Strasbourg, France). Briefly, kidney sections were digested by proteinase K followed by H_2O_2-inactivation of endogenous peroxidase. The sections were incubated with residues of deoxigenin nucleotide and terminal deoxynucleotide transferase (which catalyses a template-independent addition of deoxyribonucleotide triphosphate to the 39-end of double single-stranded DNA). The sections were then incubated with the antidegoxygenin antibody coupled to peroxidase. The cells with evidence of nuclear DNA fragmentation could be identified after incubating the sections with DAB and H_2O_2, and the LI calculated. The number of TUNEL positive cells was determined in the tubular epithelial cells both in cortex and medulla. More than 1000 tubular epithelial cells per patient were counted and cells were considered as positive when the staining intensity was moderate to strong.

Statistical analysis

Statistical Package for Social Sciences for Windows 16.0 (SPSS Inc. Chicago, IL) program was used to analyze all the data. All values are presented as the mean ± the standard error of means (SEM). Normal distribution of research data were analyzed with Kolmogorov–Smirnov test. For comparison among the groups with normal distribution, a one-way analysis of variance (ANOVA) and post hoc Tukey's test was performed. In cases where the variables do not fit with the normal distribution the Kruskal–Wallis test was used. If there was a statistically significant difference between these groups, then Mann–Whitney *U* test was applied with Bonferroni correction. A value of $p < 0.05$ was considered statistically significant.

Results

None of the rats died before termination of the study.

Biochemical analysis

There was no statistically significant difference between groups in terms of serum creatinine level in collected blood samples after euthanasia. Group 3 had the highest mean Cys-C value, as seen in Fig. 2. Cys-C value of group 4 was significantly lower compared to group 3.

Serum BUN and CRP levels were similar between the groups. TOS values were higher in the groups 3 and 4 compared to control group, but there was no difference in TOS activity with Dexp administration. TAS activity was significantly lower in contrast-induced groups 3 and 4 compared to the control group, and the expected increase in TAS activity was not detected in the 4th group in which Dexp was administered.

Serum SOD and GPx activity remained unchanged in group 3 and 4 compared to control and Dexp group. MDA levels increased significantly ($p < 0.001$) in the CIN group compared with the control, but also this parameter remained unchanged during Dexp treatment in group 4 (Table 1).

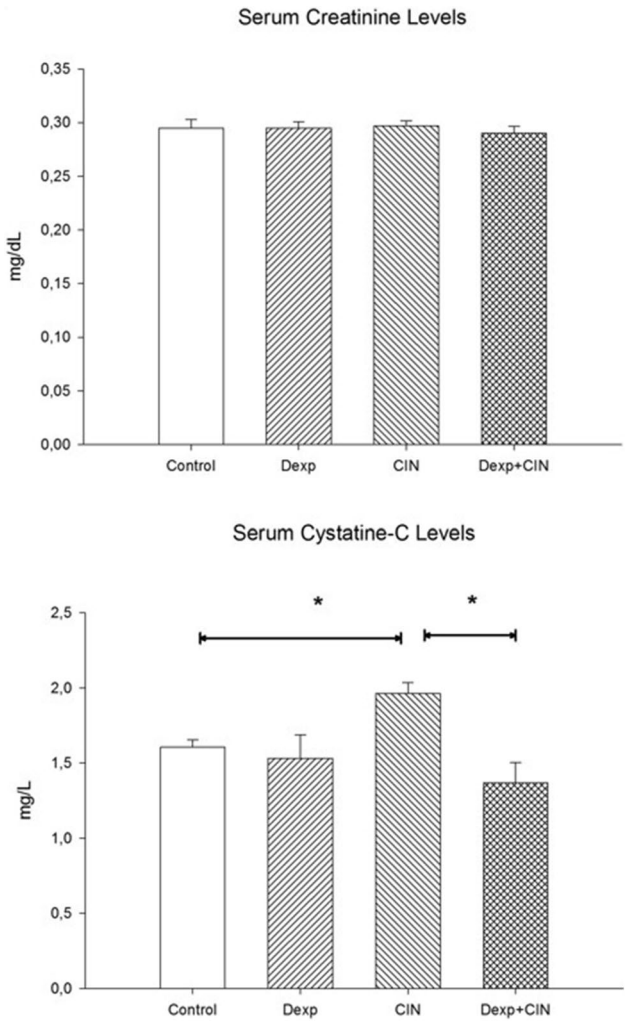

Fig. 2 Serum creatinine levels are not different from each other in all groups. Cys-C levels are only higher in CIN group than the others (*$p < 0.05$). Significant differences of measurement traits were analyzed using one-way ANOVA, followed by Tukey HSD post hoc analysis

Histological analysis

Histopathological changes were examined under the titles of apoptosis index, tubular necrosis, acute tubular injury, peritubular congestion, medullary congestion, glomerular congestion and interstitial congestion, and the results are shown in Figs. 3 and 4. The results of acute tubular necrosis and acute tubular injury analysis, which are the most important histological changes in contrast nephropathy, revealed that the group 3 has significantly higher severity of nephropathy compared to the group 4. The difference was found statistically significant ($p < 0.05$). Group 3 showed more significant pathological changes in terms of acute tubular injury, acute tubular necrosis and apoptosis compared to all other groups. Dexp administration along with contrast agent administration results in marked decrease in both acute tubular injury and acute tubular necrosis and also kidney damage is minimized (group 4). Apoptosis index median value of the group 3 was found as 17.5 while the group 4 was found as 10, relatively lower than group 3, but the difference was not statistically significant. Although peritubular, medullary and interstitial congestion were more prominent in rats undergoing contrast nephropathy, these three type of pathological changes were similar between all groups statistically (Table 2).

Discussion

Contrast induced nephropathy has become a frequent complication that creates difficulty in patient management. It is the third most common cause of hospital-acquired acute kidney injury etiology in the study conducted by Gleeson et al. [3]. Some of the risk factors are dehydration, congestive heart failure, chronic kidney disease, advanced age, contrast agent's osmolality, contrast volume and use of concomitant nephrotoxic agents [2, 18, 19]. To prevent CIN, it is necessary to establish the pathophysiological mechanism first. Although the mechanism is not fully established, one of the suggested culprit is renal medullary hypoperfusion [20]. It has been shown that contrast media reduces renal blood flow and causes ischemic reperfusion injury through

Table 1 The effects of dexpanthenol on biochemical values

	Control (group 1)	Dexp (group 2)	CIN (group 3)	Dexp + CIN (group 4)	*P* value ANOVA
Serum blood urea nitrogen (mg/dl)	18 ± 0.5	19 ± 0.7[a]	18 ± 0.9[a]	18.6 ± 0.8[c]	ns
Serum creatinine (mg/dl)	0.29 ± 0.1	0.29 ± 0[a]	0.29 ± 0[a]	0.29 ± 0.1[c]	ns
Cystatin C (mg/L)	1.6 ± 0.1	1.5 ± 0.3[a]	1.96 ± 0.1[b]	1.36 ± 0.3[d]	< 0.05
CRP (mg/L)	0.11 ± 0.1	0.1 ± 0.01[a]	0.1 ± 0.01[a]	0.1 ± 0.01[c]	ns
SOD (ng/ml)	11.5 ± 3.1	9.8 ± 2.8[a]	13.4 ± 3.7[a]	12.6 ± 3.8[c]	ns
GSH-Px (ng/ml)	29.5 ± 3.9	32.5 ± 6.3[a]	33.3 ± 3.8[a]	33.2 ± 3.0[c]	ns
MDA (nmol/ml)	27.4 ± 2.7	36.3 ± 4.0[a]	34.7 ± 5.1[b]	35.5 ± 5.5[c]	< 0.05
TOS (μmol/L)	5.7 ± 1.1	4.5 ± 1.8[a]	11.4 ± 3.5[b]	15.7 ± 6.2[c]	< 0.05
TAS (mmol/L)	0.97 ± 0.2	0.58 ± 0.2[a]	0.47 ± 0.2[b]	0.45 ± 0.34[c]	< 0.05

Data are expressed as means ± SDs. Significant differences of measurement traits were analyzed using one-way ANOVA, followed by Tukey HSD post hoc analysis

ns not significant

[a] $p > 0.05$ vs control, [b] $p < 0.05$ vs control, [c] $p > 0.05$ vs group 3, [d] $p < 0.05$ vs group 3

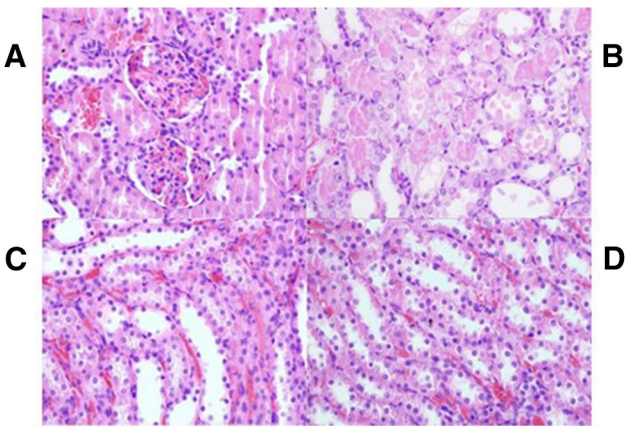

Fig. 3 Light microscopic changes in kidney parenchyma of 4 different groups, H&E 400×: **a** Control group; light microcopy is unremarkable, **b** CIN group; prominent tubular necrosis is present, **c** dexpanthenol group; mild medullary congestion is present, **d** group 4 (Dexp + CIN); mild medullary congestion is present (Note that light microscopic features of Dexp group and Dexp + CIN are similar)

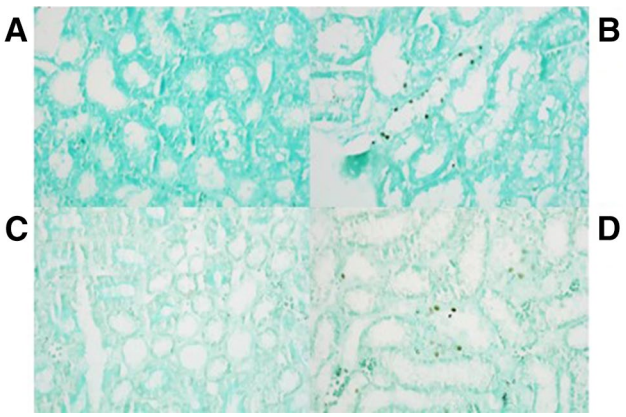

Fig. 4 Nuclear DNA fragmentation by immunoperoxidase staining seen as black to brown nuclear staining of tubular epithelial cells in 4 different groups; **a** control group, **b** contrast group, **c** Dexp group, **d** Dexp + CIN group (note that labeling indexes of Dexp and Dexp + CIN groups are similar)

renal artery vasoconstriction [20]. However, administration of iohexol alone in rats did not cause nephropathy and some other drugs were administered along with contrast agent to improve the nephropathy such as L-NAME, non-steroidal anti-inflammatory drug (NSAID) and glycerin [16, 21]. In this study, we aimed to achieve renal ischemia and contrast-induced nephropathy with a combined model of 3 days water restriction, then injecting L-NAME and tenoxicam and finally the contrast agent.

This study was based on the hypothesis that antioxidant activity of Dexp may help to prevent CIN. The hypothetical preventive effect of Dexp on CIN was shown histologically. This study revealed that administering Dexp both prior to and after contrast media application could reduce acute tubular necrosis and acute tubular injury, which are the characteristic features of contrast nephropathy. At the same time, serum Cys-C levels, not serum creatinine, elevated with accompanying all these tubular injury were reduced significantly by dexpanthenol application for 5 days. Cys-C is a monoglycosylated protein that is produced by all nucleated cells and is almost completely reabsorbed and catabolized by proximal tubular cells. Serum Cys-C levels seems to be more sensitive than serum creatinine to evaluate kidney injury and considered as alternative marker for use in kidney functions [22]. In our study, serum creatinine levels remained unchanged even when acute tubular damage was evident in CIN group but serum Cys-C levels were significantly increased like as an early marker in group 3. High Cys-C levels were not observed in the Dexp + CIN group. Pretreatment with dexpanthenol prevented high level

Table 2 Effects of dexpanthenol on histopathological data

	Control (group 1)	Dexp (group 2)	CIN (group 3)	Dexp + CIN (group 4)	*P* value
Apoptosis index	0	1.8 ± 3.1	16.5 ± 5.2[b] (median: 17.5)	17 ± 16.1[c] (median: 10)	< 0.05
Acute tubular necrosis	0	0	0.83 ± 0.9[b] (median: 1)	0[d]	< 0.05
Acute tubular injury	0	0	1.67 ± 0.8[b]	0[d]	< 0.05
Medullary congestion	1 ± 0	1.17 ± 0.4	1.33 ± 0.5[a]	1.17 ± 0.4[c]	ns

For histopathological score, data are expressed as means ± SDs and median. Significant difference of measurements between all groups were analyzed using Kruskal–Wallis variance analysis and then Mann–Whitney *U* test for apoptotic index and acute tubular necrosis scores. One-way ANOVA, followed by Tukey HSD post hoc analysis were used for acute tubular injury and medullary congestion data

ns not significant

[a]$p > 0.05$ vs control, [b]$p < 0.05$ vs control, [c]$p > 0.05$ vs group 3, [d]$p < 0.05$ vs group 3

of cystatin C by reducing tubulary injury and necrosis, as seen Fig. 2. While both acute tubular damage and injury and also apoptosis were evident in group 3, pretreatment with dexpanthenol (in group 4) reduced these damages.

Pathophysiology of CIN can be explained on three distinct, but interacting mechanisms: medullary ischaemia, formation of reactive oxygen species and direct tubular insult [6, 23–26]. After contrast agent injection, vasoconstriction agents such as endothelin and adenosine are increased and renal perfusion is impaired. Acute tubular necrosis may occur due to decreased blood flow. Increased reactive oxygen metabolites and renal ischemia may also cause nephropathy [6]. In addition, high contrast media viscosity increases plasma viscosity, which in turn produces medullary hypoperfusion and renal tubular obstruction (by concentrated urine), being ultimately responsible for tubular destruction. In this way, the hemodynamic effects of the contrast agent and the excess viscosity impair the renal perfusion [6]. Dexp is a pantothenic acid derivative that increases intracellular ATP, glutathione and acetyl CoA activity in tissues [7]. In a rat study evaluating amikacin-induced nephropathy conducted by Doğan et al., levels of SOD and TAS were increased in rats treated with Dexp [27]. Significant elevation in SOD and TAS levels were also detected in another study of renal ischemia reperfusion model with Dexp [7]. Although our study was not able to show all those changes, the proven positive effect of Dexp on biochemical data by other nephropathy studies supports our thesis. In group 3 and 4, where contrast-induced nephropathy was created, TOS activity was found significantly higher compared to control group and Dexp group. Those high TOS levels in groups 3 and 4 result from the effect of the contrast-induced nephropathy model in both groups. Similarly, MDA elevation in tissue or blood is an indicator of an increase in lipid peroxidation due to nephrotoxicity. In our group 3 (CIN), a significant increase was observed in MDA levels compared with the controls. But, decreasing MDA and also TOS levels as expected was not observed with dexpanthenol therapy (Dexp + CIN) compared with the CIN group. TAS activity did not reach to the expected level in group 4. Nonetheless, serum Cys-C levels and histopathological aspects improved with dexpanthenol treatment in CIN model. This suggests that the favorable effect of Dexp in this CIN model may also be mediated through other mechanisms independent of antioxidant pathways such as some favorable effects on medullary ischemia or direct tubular toxicity. Further studies are needed to prove this hypothesis. In addition, since the variability of oxidant and antioxidant reactions in the renal tissue is very rapid, the values obtained from blood samples on the 2nd day following CIN may not reflect the moment of actual change.

The apoptosis index was also assessed in our study and was found higher in the group 3. Apoptosis in kidney tissue originate from the increase in some enzymatic activities (caspase, calpains…), which is activated by intracellular calcium change. In literature, it has also reported that apoptotic effects are related to the acetylation of pro-apoptotic proteins such as p53, NF-KB, and FOXO. Some molecules like astaxanthin, inhibit this acetylation via upregulate of SIRT-1 activity catalyzing the deacetylation of p53, and decrease p53 activity. Thus, cell apoptosis and DNA damage are thought to decrease [28]. In our study, although the difference was not statistically significant ($p = 0.08$) apoptotic activity was found lower in group 4 than group 3. Dexp appears to have a little effect on intracellular apoptotic activity. We do not know in which ways Dexp acts on apoptotic activity. This work is not designed to investigate this.

The most important limitation of our study is lack of blood samples regarding later period (at 3rd days after radiocontrast exposure) following contrast-induced nephropathy modeling. We speculate that histopathological data especially in group 3 may have more prominent effect on serum creatinine levels in the late period. Although the antioxidant effect of Dexp is well-known and its histological protective effect has been proved by this study, we could not demonstrated its antioxidant effects of dexpanthenol. In this context, an additional limitation of the study was the lack of evaluation of the effect of different dexpanthenol doses on

nephropathy. This dose was chosen as it is more effective to use 500 mg in rat studies [7, 11]. Nevertheless, additional studies with different doses of dexpanthenol will allow for clearer evaluations its effects especially on antioxidant activity.

Conclusion

In this study, the preventive effect of Dexpanthenol on contrast-induced nephropathy was pathologically proven. Marked regression was established in acute tubular injury and necrosis through intraperitoneal administration of Dexp, 500 mg/kg/day for 5 days. The fact that dexpanthenol is effective in preventing contrast nephropathy in humans can not be concluded from this study, but our results give positive findings in this direction and give hope. This agent needs to be investigated of its beneficial mechanisms on histology of CIN and other studies are required in rats. In addition, further experimental studies with different doses of dexpanthenol administration could be planned to demonstrate the antioxidant effects of it.

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to declare.

Ethical approval Experiments were performed in accordance with the criteria about the care and use of Laboratory Animals of Gazi University Local Ethics Committee.

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