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Adjunctive Oral Methylprednisolone in Pediatric Acute Pyelonephritis Alleviates Renal Scarring

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WHAT'S KNOWN ON THIS SUBJECT: Renal scarring after acute pyelonephritis is associated with long-term sequelae. Preventing scarring after acute pyelonephritis depends not only on early diagnosis and rapid treatment to eradicate the bacteria but also ameliorating the destructive inflammatory response.

WHAT THIS STUDY ADDS: In this study, an adjunctive short course of oral methylprednisolone therapy significantly reduced the occurrence and/or severity of renal scarring after acute pyelonephritis in children.

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KEY WORDS
glucocorticoid, acute pyelonephritis, renal scar, pediatric

ABBREVIATIONS
UTI—urinary tract infection
APN—acute pyelonephritis
GC—glucocorticoid
MPD—methylprednisolone sodium phosphate
DMSA—technetium-99m–labeled dimercaptosuccinic acid scan
VUR—vesicoureteral reflux
VCUG—voiding cystourethrogram
OR—odds ratio
CI—confidence interval
TLR—Toll-like receptor

This trial has been registered at Cheng Kung University Medical College and Hospital (registration No. NCKUH-BR-90-035).

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abstract

OBJECTIVE: To determine if glucocorticoids can prevent renal scar formation after acute pyelonephritis in pediatric patients.

METHODS: Patients younger than 16 years diagnosed with their first episode of acute pyelonephritis with a high risk of renal scar formation (ie, inflammatory volume ≥ 4.6 mL on technetium-99m–labeled dimercaptosuccinic acid scan [DMSA] or abnormal renal ultrasonography results) were randomly assigned to receive either antibiotics plus methylprednisolone sodium phosphate (1.6 mg/kg per day for 3 days [MPD group]) or antibiotics plus placebo (placebo group) every 6 hours for 3 days. Patients were reassessed by using DMSA 6 months after treatment. The primary outcome was the development of renal scars.

RESULTS: A total of 84 patients were enrolled: 19 in the MPD group and 65 in the placebo group. Patient characteristics were similar between the 2 groups, including the acute inflammatory parameters and the initial DMSA result. Renal scarring was found in 33.3% of children treated with MPD and in 60.0% of those who received placebo ($P < .05$). The median cortical defect volumes on follow-up DMSA were 0.0 mL (range: 0–4.5 mL) and 1.5 mL (range: 0–14.8 mL) for the MPD and placebo groups, respectively ($P < .01$). Patients in the MPD group experienced faster defervescence after treatment than the placebo group.

CONCLUSIONS: Adjunctive oral MPD therapy reduced the occurrence and/or severity of renal scarring after acute pyelonephritis in these hospitalized children who had a high risk of renal scar formation. *Pediatrics* 2011;128:e496–e504

Urinary tract infections (UTIs) are a common problem in children. Nearly two-thirds of patients with febrile UTIs have acute pyelonephritis (APN).[1,2] Renal scarring after APN is a concern with long-term sequelae, including hypertension, impaired renal function, toxemia of pregnancy, and end-stage renal failure.[3–7] The incidence of renal scarring after APN ranges from 26.5% to 57%.[2,8] Some have shown that inflammatory processes, rather than the bacterial component of APN, are responsible for permanent renal tissue damage.[9–11] Therefore, preventing renal scarring after APN depends not only on an early diagnosis and rapid and effective treatment but also on ameliorating the destructive inflammatory response.

Animal studies have assessed various antiinflammatory modalities to prevent scarring after APN. For example, cyclophosphamide,[12] cobra venom factor,[13] superoxide dismutase,[14] angiotensin II type 1 receptor antagonist,[15] melatonin,[16] and oxytocin[17] all reportedly reduce the occurrence of scarring after APN. Ibuprofen[18] and dapsone[19] also resulted in significant inhibition of renal scarring in animal models. In human medicine, most of these medications are not clinically available because of their toxicity and possible adverse events.

In contrast to the aforementioned agents, glucocorticoids (GCs) have been clinically useful for the treatment of various infectious diseases such as bacterial meningitis.[20–23] Antibiotics combined with GCs reportedly prevent renal scarring in experimental animal models of APN.[24–26] Urinary concentrations of interleukin-6 and interleukin-8 are reduced in cases of APN treated with a combination of antibiotics and dexamethasone.[27] Given these findings, this study was conducted to determine if a short course (3 days) of methylprednisolone sodium phosphate (MPD) could prevent renal scarring in children diagnosed with a serious APN.

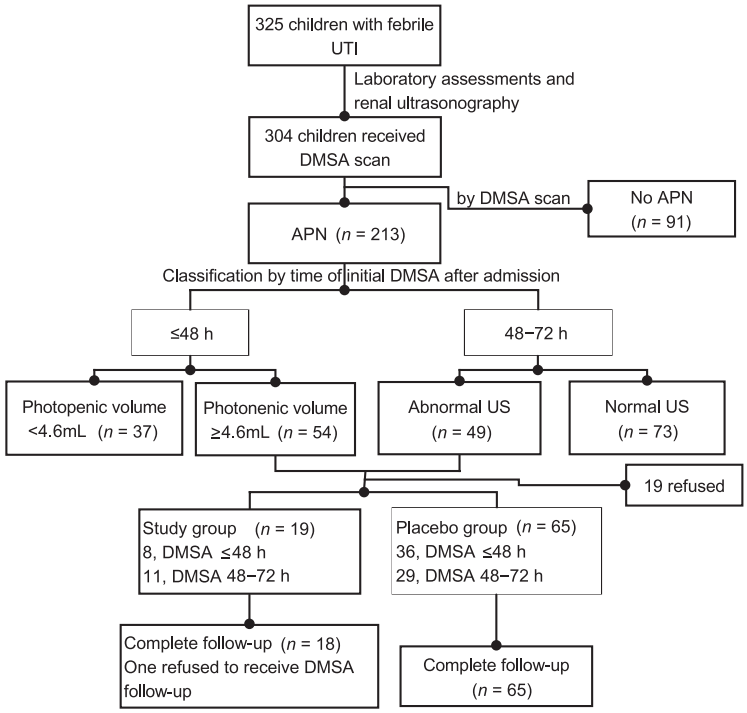

FIGURE 1
Study participant flow diagram. US indicates ultrasonogram.

METHODS

Study Population

Children diagnosed with their first febrile UTI admitted between January 2002 and December 2004 were screened for enrollment in this double-blind, placebo-controlled prospective study (Fig 1). Patients were included if: they were between 1 week and 16 years of age; had evidence of UTI (ie, a core temperature of ≥38°C, positive urine culture, growth of microorganisms $\geq 10^5$ colony-forming units per mL from a clean, voided midstream urine in older children or $\geq 10^3$ colony-forming units per mL after bladder catheterization or any growth from a suprapubic puncture in younger children; and ≥5 leukocyte cells per high-power field); and if they were at high risk of renal scar formation. Children were considered at risk for renal scar formation if either a focal or multifocal photon defect with a maximal inflammatory volume of ≥4.6 mL on technetium-99m–labeled dimercaptosuccinic acid scan (DMSA) performed within 48 hours of admission was noted[28] or there was an abnormal finding on renal ultrasonography,[29] if DMSA was performed to diagnose APN between 48 and 72 hours after admission. Exclusion criteria included: a history of UTI; previous treatment with either oral or intravenous antibiotics; there was concurrent urogenital uropathy (except vesicoureteral reflux [VUR]); DMSA was not performed within 72 hours of admission; and there was no photopenic finding or diffuse photopenic kidney on DMSA or space-occupying lesions on ultrasonography, except those progressing to abscess formation.

This study was approved by the institutional review board and human ethics committee of the National Cheng Kung University Medical Hos-

pital. Informed parental consent was also obtained.

Imaging Studies

Ultrasonography was arranged immediately for any child admitted to the hospital with clinical signs of a febrile UTI. Renal parenchymal changes on ultrasonography can indicate extensive renal inflammation.[29] All ultrasonography procedures were performed using a Nemio 30 SSA-550A (Toshiba Medical Systems Ltd, Crawley, West Sussex, United Kingdom) unit equipped with a convex probe in B mode by trained pediatric nephrologists. Ultrasonographic images were classified as abnormal if any of the following features were observed: parenchymal hyperechogenicity; hypoechoic or hyperechoic focal lesion(s); or significant increase in kidney length or width compared with the opposite kidney and the normal range for children of the same age.

Dimercaptosuccinic acid scans were performed using the same protocol as previously described.[28] The inflammatory volume of photopenic areas on the initial DMSAs was calculated by an experienced nuclear medicine physician (Dr Chiu), who was blinded to the patients' clinical information. When multiple foci of inflammation were observed on the DMSAs, only the largest inflammatory volume was calculated and used in this study.[28] Patients diagnosed with APN underwent a follow-up DMSA a minimum of 6 months later to confirm renal scarring.[30]

A voiding cystourethrography (VCUG) was performed 2 to 4 weeks after the diagnosis of APN, once the acute infection had subsided. The presence of VUR was graded according to the system of the International Reflux Study in Children.[31]

Treatment Protocol

Urine and blood samples were collected from all patients before initiating treatment. Empirical parenteral antibiotic treatment involved intravenous cephalothin (100 mg/kg per day; Ulothin [U Liang Chemical and Pharmaceutical, Taoyuan, Taiwan]) every 6 hours and intravenous gentamicin (5 mg/kg per day) (Yung Shin Pharmaceutical Industrial, Taichung, Taiwan) delivered over a period of 30 minutes every 12 hours for a minimum of 3 days.

Patients classified as high risk for renal scarring (as determined by inflammatory volume on DMSA and/or abnormal ultrasonography results) were enrolled in the study and administered either oral MPD (MPD group) or a placebo (placebo group) for 3 days in a double-blind manner with a ratio of ~1:3 that was justified on ethical grounds. Patients were removed from the study if an abnormal result on ultrasonography was followed by a normal reading on the DMSA. A computer-generated list of random therapy assignments was used, and the code was not broken until the completion of the study. The total daily dosage of oral MPD (1.6 mg/kg per day, maximum of 48 mg/day; Excelin [Winston Pharmaceutical, Yong Kang, Taiwan]) was administered in divided doses every 6 hours.

Antibiotic regimens were adjusted according to bacterial susceptibility test results. Parenteral antibiotics were changed to the oral form and patients were discharged once they had been afebrile for 48 hours. Oral antibiotics were prescribed for approximately an additional 14 days, then a low dose of trimethoprim or cephalothin was prescribed until a VCUG was performed 2 to 4 weeks later. At least 1 negative urine culture result was required to complete the treatment course. Regular outpatient clinic follow-up was arranged for all patients. Urinalyses and urine cultures were performed 1, 3, and 6 months after hospital discharge, except for patients with VUR, who were followed up monthly.

Clinical Laboratory Assessment

Blood cultures were obtained at the time of hospitalization and again after 48 hours of therapy if the patients were bacteremic. White blood cell counts and C-reactive protein levels were also measured.

Statistical Analysis

Continuous data were expressed as median (range) or mean ± SD, and differences between groups were analyzed by using the Mann-Whitney *U* test. Differences between the groups in the frequencies of various findings were tested by using either the χ^2 test or Fisher's exact test. Frequencies of complication were analyzed by using relative risk. Incidence of complications was identified in the study protocol as the primary variable with which to assess the effect of MPD. In univariate and multivariate analyses, the odds ratio (OR), 95% confidence interval (CI), and statistical associations were calculated and adjusted to estimate risk of renal scarring in relation to the treatment and clinical parameters. Statistical analysis was performed by using SPSS 15.0 (SPSS Inc, Chicago, IL). A P value of $<.05$ was considered statistically significant.

RESULTS

During the study period, 325 pediatric patients diagnosed with their first febrile UTI were screened for enrollment. Of these, 304 underwent DMSA. Patients with an inflammatory volume of ≥4.6 mL after DMSA or with renal parenchymal changes noted using ultrasonography were enrolled consecutively. In total, 91 children underwent DMSA within 48 hours of admission, and 122 underwent DMSA within 48 to

TABLE 1 Demographic and Clinical Characteristics of the 84 Study Participants

Characteristic	Placebo Group ($N = 65$)	MPD Group ($N = 19$)	*P*
Age, median (range), mo	8 (1–180)	87 (1–168)	.80
Gender, male, *n* (%)	34 (52.3)	10 (52.6)	.98
Maximal body temperature, median (range), °C	39.3 (36.6–41.2)	39.9 (38.5–42.0)	.06
Fever duration before admission, median (range), d	2 (1–7)	3 (0–5)	.70
Preterm history, *n* (%)	1 (1.5)	2 (10.5)	.06
Breastfeeding during the enrolled period, *n* (%)	7 (10.8)	2 (10.5)	.98
Noncircumcision of male children, *n* (%)	31 (91.2)	8 (80.0)	.33
VUR, *n*/*N* (%)	14/60 (23.3)	6/17 (35.3)	.32
Unilateral, *n*/*N* (%)	10/14 (71.4)	6/6 (100)	.73
Bilateral, *n*/*N* (%)	4/14 (28.6)	0/6 (0)	
White blood cell count, median (range), $\times 10^9$/L	18.3 (4.1–34.1)	15.8 (7.2–28.8)	.09
Shift to left of white blood cell count, median (range), %	62 (14–96)	66 (46–90)	.26
C-reactive protein, median (range), mg/L	86.0 (6.0–313.7)	92.0 (14.5–204.7)	.53

Continuous data are presented as median (range); differences were analyzed with the Mann-Whitney *U* test. Categorical data are presented as number (%); differences were analyzed with the χ^2 test.

72 hours. Ultimately, 103 patients met the inclusion criteria and were considered at high risk of renal scar formation.[28,29] Of these, 19 declined to participate. The remaining 84 patients were enrolled and randomly assigned to either the MPD group (antibiotics plus MPD) or the placebo group (antibiotics plus placebo).

Demographic and Clinical Characteristics

Of the 84 children enrolled in the study, 19 were assigned to the MPD group and 65 to the placebo group. The MPD group consisted of 10 boys and 9 girls (median age: 7 months [range: 1–168 months]; mean ± SD age: 24.6 ± 41.4 months) and the placebo group consisted of 34 boys and 31 girls (median age: 8 months [range: 1–180 months]; mean ± SD age: 20.0 ± 32.4 months).

The characteristics of the study participants are summarized in Table 1. A high incidence of noncircumcision was noted in the male participants (MPD versus placebo: 8 of 10 vs 31 of 34; $P = .33$). Of the 84 patients, 77 (91.7%) underwent VCUG. No significant differences were found between the 2 groups in terms of age, gender distribution, duration of fever before admission, history of breastfeeding, or prevalence of VUR. In addition, no statistically significant differences were found between the 2 groups in clinical inflammatory parameters, including degree of peripheral leukocytosis, left shift of the white blood cell count, and C-reactive protein level (Table 1).

In total, 83 of 84 (98.9%) patients underwent a follow-up DMSA at a median of 8 months after the initial diagnosis (range: 6–38 months). One patient in the MPD group (initially diagnosed with bilateral APN via DMSA) was lost to follow-up. Patients in the MPD group experienced faster defervescence after treatment than those in the placebo group (median: 2 [range: 0–3] vs 2 [range: 0–8] days; $P < .05$; Fig 2).

Escherichia coli was the most common uropathogen, accounting for infections in 17 of 19 (89.5%) patients in the MPD group and 55 of 65 (84.6%) patients in the placebo group ($P > .05$). *E coli* bacteremia was found in 3 patients: 2 in the placebo group and 1 in the MPD group.

The results of initial DMSA showed no significant difference in inflammatory volume between groups (Table 2). In terms of renal units, the rates of APN-affected kidneys in the placebo and MPD groups were 55.4% (72 of 130) and 52.6% (20 of 38), respectively ($P = .76$). The median inflammatory volume was 6.0 mL (range: 1.0–103.0 mL) in the placebo group and 4.0 mL (range: 1.4–34.6 mL) in the MPD group ($P = .07$) (Table 2, Fig 3A).

Incidence and Extent of Renal Scarring

Patients in the MPD group had a lower rate and extent of renal scar formation than those in the placebo group (Table 2, Fig 3, A and B).The incidences of re-

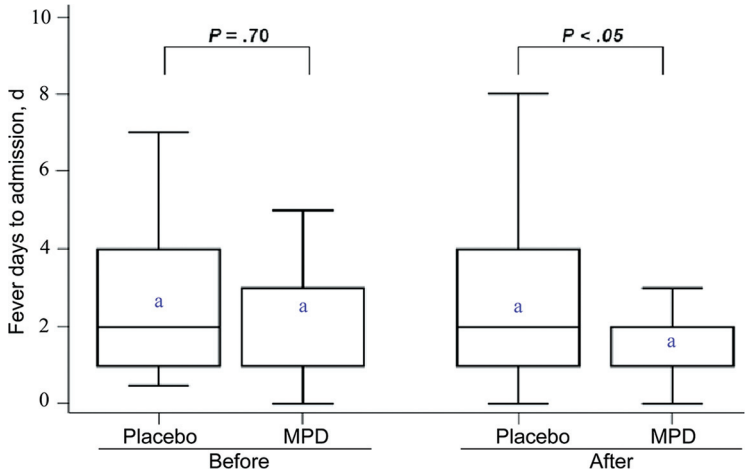

FIGURE 2
Duration of fever before and after admission in the placebo ($N = 65$) and MPD ($N = 19$) groups. [a] A significant difference was found between the 2 groups in duration of fever after admission (median: 2 vs 3 days [$P = .7$], before admission; 2 vs 2 days [$P < .05$], after admission).

TABLE 2 Initial and Follow-up DMSA Results

Variable	Placebo Group	MPD Group	*P*
Initial DMSA			
Patients, *N*[a]	65	19	
Right or left maximal inflammatory volume of patients, median (range), mL	6.1 (1.0–103.0)	4.1 (1.4–34.6)	.09
Renal units, *N*[b]	130	38	
Rate of APN kidneys, %	72/130 (55.4)	20/38 (52.6)	.76
Inflammatory volume of APN-affected kidneys, median (range), mL	6.0 (1.0–103.0)	4.0 (1.4–34.6)	.07
Follow-up DMSA			
Patients, *N*[a]	65	18	
Patients with scar formation, *N* (%)	39 (60.0)	6 (33.3)	<.05
Right or left maximal cortical defect of patients, median (range), mL	1.1 (0–14.8)	0 (0–4.5)	<.05
Renal units, *n*[b]	72	18	
Kidneys with scar formation, *n* (%)	46 (63.9)	6 (33.3)	<.05
Volume of cortical defect in each kidney, median (range), mL	1.5 (0–14.8)	0 (0–4.5)	<.01

[a] Total number of patients: placebo group, $N = 65$ in acute and scar-formation stages; MPD group with 1 patient lost to follow-up, $N = 19$ in acute stage and $N = 18$ in scar-formation stage.
[b] Number of affected kidneys.

nal scarring after APN were 33.3% and 60.0% in the MPD and placebo groups, respectively ($P < .05$). A significant difference was found between the 2 groups in the maximal photopenic area during the scar-formation stage (median: 0 [range: 0–4.5] vs 1.1 [range: 0–14.8] mL; $P < .05$) (Table 2). In terms of renal units, the incidences of renal scarring after APN were 33.3% (6 of 18) and 63.9% (46 of 72) in the MPD and placebo groups, respectively ($P < .05$) (Table 2, Fig 3B). A significant difference was found in the volume of renal scarring in terms of renal units (median: 0 vs 1.5 mL; $P < .01$) (Table 2, Fig 3A).

Risk Factors for Renal Scar Formation

Risk factor analysis for renal scar formation in the placebo and MPD groups was performed by using univariate and multivariate analyses (Table 3). The initial inflammatory volume on DMSA was a risk factor for renal scar formation in the placebo group (OR: 1.13 [95% CI: 1.02–1.25]) but not in the MPD group (OR: 1.06 [95% CI: 0.72–1.55]). No other clinical parameters predicted scar formation in either group.

DISCUSSION

This study revealed that the antiinflammatory drug MPD, when combined with antibiotic agents, can ameliorate both clinical parameters and renal scar formation in pediatric patients with APN. The clinical implications and possible mechanisms are supported by results of animal studies and significant decreases of proinflammatory cytokine levels in patients with APN.[24–27] In addition, the shorter duration from time of admission to defervescence can reduce the duration of hospitalization and costs. Thus, the combination of MPD and antibiotics seems to be a cost-effective approach to the management of APN in children.

In this study, the rates of renal scarring in the placebo group in terms of patients and in terms of renal units were 60.0% and 63.9%, respectively. It is noteworthy that these rates are higher than those reported in previous studies. One meta-analysis found a higher incidence of renal scarring after APN in Asia, both in terms of patients and in terms of renal units.[8] Geographic variation in this finding is supported by other studies.[2,28,29,32–35] In addition to geographic variation, the difference in renal scarring rates may also be related to our study enrolling patients who had a high risk of subsequent renal damage.

The treatment effects of GCs need to be weighed against their adverse effects because the use of GCs in combination therapy may produce other adverse effects, as shown in previous studies.[36–39] It is important to note, however, these adverse effects were specific to infants with very low and extremely low birth weights. For term infants and children who received short courses of GCs, the adverse effects seemed relatively limited. In our study, no significant adverse effects of MPD were observed and the use of GCs did not affect bacterial sterilization. No recurrence or relapse in UTI was found during the follow-up period (10.1 ± 6.6 months). Other researchers have also found that administration of GCs combined with antibiotics in the treatment of APN did not influence the mean bacterial clearance time.[27] The safety of GC combination therapy is supported by the safety of short courses of oral steroids in the treatment of hospitalized children with asthma exacerbations, croup, and bronchiolitis.[40–43] All of the abovementioned results demonstrate the safety of short courses of oral GCs in children, even those younger than 1 year.

Permanent renal damage as a consequence of APN is caused by the inflammatory process.[9–11] Although the molecular mechanisms underlying the antiinflammatory and immunosuppressive effects of GCs are complex, the signaling pathways of Toll-like receptors (TLRs) are postulated as targets for mediating such effects.[44–48] TLRs are expressed in kidneys and play a key role in recognizing bacterial components, known as pathogen-associated molecular patterns, and

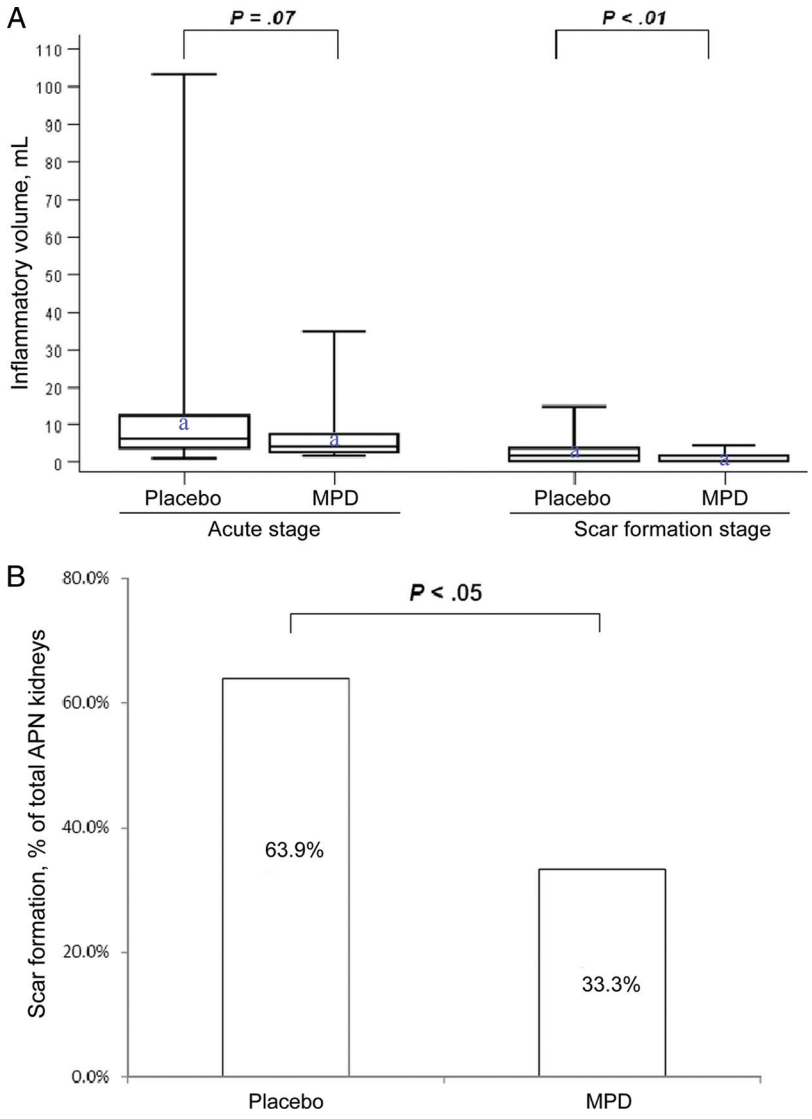

FIGURE 3

Inflammatory volume and scar formation. A, Inflammatory volume in the acute and scar-formation stages in the placebo ($n = 72$) and MPD ($n = 20$ in acute stage; $n = 18$ in scar-formation stage) groups. [a] Median value. B, Rate of scar formation in the placebo ($n = 72$) and MPD ($n = 18$) groups.

activating signaling pathways that lead to the production of cytokines/chemokines to attract polymorphonuclear leukocytes to the site of inflammation.[49–51] Inhibition of TLR signaling is likely to be central in the manifestation of the remarkable antiinflammatory and immunosuppressive effects of GCs via a variety of molecular mechanisms.[44,46,47,52–54] GCs also reduce collagen synthesis by decreasing the binding of the transforming growth factor β activator protein complex to the transforming growth factor β element in the promoter of the proa1 (type I) collagen gene, preventing the assembly of type I collagen.[55] Thus, GCs regulate not only early inflammatory cascades but also late collagen synthesis. Therefore, adjunctive therapy with GCs may prevent renal fibrosis after APN.

Various new methods to prevent renal scarring tested in animal studies include an angiotensin II type I antagonist,[15] melatonin,[16] oxytocin,[17] and leukotriene receptor antagonist.[56] To obtain maximal reduction in pathologic glomerular transforming growth factor β1 overexpression and matrix accumulation, doses of losartan need to be higher than those known to control blood pressure.[15] This dose-dependent antifibrotic effect of losartan therefore makes clinical application difficult. Drugs that ameliorate oxidative renal injury in rats with APN include melatonin,[16] oxytocin,[17] and montelukast.[56] Melatonin has been investigated in rat models, but the safety in children is not well studied.[16] Oxytocin alleviates oxidant renal injury in rats with APN via its antioxidant actions. The clinical experience with oxytocin in pediatrics is currently limited, and the parenteral routes of administering oxytocin make it clinically inconvenient.[17] Montelukast blocks the action of leukotriene D_4 to decrease renal inflammation and renal scar formation by reversing the oxidative effects of *E coli*.[56] These findings suggest that antileukotriene drugs may have a role in the treatment of APN; however, montelukast is expensive and the possible neuropsychiatric adverse effects limit its application. In comparison, treatment of APN-affected children with a short course and median dosage of GCs is safe and devoid of significant adverse effects.

An important consideration is the appropriate patient age for which treatment of APN with MPD combination therapy should be recommended. Our study revealed that renal scarring after APN was equally prevalent in 3 age groups in the placebo arm ($<$1 vs 1–5 vs $>$5 years: 60.8% vs 69.2% vs 75.0%, respectively; $P > .05$). The incidence of renal scarring after APN in neonates ($\leq$1 month) was relatively low in our study ($\leq$1 vs 1–3 vs 3 months to 1 year: 28.6% vs 80.0% vs 56.7%, respectively). This may be a result of the different criteria for admission of newborns and patients older than 1 month

TABLE 3 Risk Factors for Renal Scarring Stratified According to Treatment Group

Risk Factor	Placebo Group ($N = 65$)			MPD Group ($N = 18$)		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.00	0.99–1.02	.84	0.99	0.96–1.02	.57
Gender						
Male	0.70	0.26–1.89	.48	0.71	0.10–5.12	.74
Female	Reference			Reference		
Maximal documented body temperature	1.38	0.70–2.72	.36	0.69	0.20–2.40	.56
Duration of fever before admission, d	1.21	0.93–1.58	.16	1.88	0.78–4.54	.16
Duration of fever after admission, d	1.23	0.90–1.68	.20	0.65	0.18–2.39	.52
C-reactive protein, mg/L	1.01	1.00–1.01	.22	1.00	0.98–1.02	.99
White blood cell count, $\times 10^9$/L	1.07	0.99–1.16	.08	0.90	0.74–1.09	.27
Left shift, %	1.03	1.00–1.06	.10	1.01	0.94–1.08	.87
Renal ultrasonography						
Normal	Reference			Reference		
Abnormal	0.94	0.32–2.75	.91	0.40	0.04–3.90	.43
Initial inflammatory volume on DMSA, mL	1.13	1.02–1.25	.02	1.06	0.72–1.55	.78
VUR						
No	Reference			Reference		
Yes	1.27	0.37–4.38	.71	3.00	0.29–31.63	.36

OR indicates odds ratio; CI, confidence interval.

according to American Academy of Pediatrics guidelines. Hiraoka et al[57] reported that early treatment should prevent renal changes. In that study, the mean duration of fever before admission in patients younger than 1 month was 0.5 day. Older patients were often admitted after a longer duration of fever, leading to more severe inflammatory effects and a higher risk of renal scar formation. Given the fact that the incidence of renal scarring after APN is high in all patients (except neonates), it seems that GC combination therapy might be beneficial to any patient older than 1 month admitted to the hospital requiring parental antibiotic treatment. Because of the limited information regarding the incidence of renal scarring after APN in neonates, additional study to support this recommendation in neonates is necessary.

The major limitation of our study is that it was conducted in a single tertiary referral center with a pioneer and small-scale design. For this reason, some of the subgroup analyses only involved small numbers of patients. As such, the conclusion should not be overextended. In addition, because the sensitivity and specificity of ultrasonography for APN are not as high as those of DMSA, another limitation of our study may be associated with the inconsistency of the method used to identify patients at high risk of renal scarring. Nevertheless, the results are promising, and additional studies with larger populations should be designed to validate these effects and determine the optimum dosage of GCs and the age of patients most likely to benefit from them.

CONCLUSION

Adjunctive oral MPD with adequate antibiotics merits further consideration as a potential treatment regimen to alleviate permanent tissue injury in admitted children with serious APN.

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