

Efficacy of Corticosteroids in Infection-Related Glomerulonephritis—A Randomized Controlled Trial



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Introduction: Infection-related glomerulonephritis (IRGN) is associated with glomerular immune complex deposition along with complement activation. Steroids may attenuate glomerular injury and thereby improve renal outcomes.

Methods: We randomly assigned patients who had biopsy-proven IRGN and serum creatinine greater than 1.5 mg/dl to receive corticosteroids plus supportive care (intervention arm), or supportive care alone (control arm). Patients were followed up for 6 months. The primary outcome was complete renal recovery at 6 months. Safety of steroid therapy was also assessed.

Results: A total of 52 patients underwent randomization. At 6 months, 17 of 26 patients (65.4%) in the intervention arm and 14 of 26 patients (53.8%) in the control arm had complete renal recovery (odds ratio 1.6; 95% confidence interval, 0.5–4.9; $P = 0.397$). There was no statistically significant difference in any of the secondary outcomes. Adverse events occurred in 12 patients (46.2%) in the intervention arm and 2 patients (7.7%) in the control arm ($P = 0.002$).

Conclusion: In this single-center trial, corticosteroids did not result in a statistically significant increase in rates of complete renal recovery at 6 months. There was a significantly increased risk of adverse events associated with the use of corticosteroids.

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KEYWORDS: infection-related glomerulonephritis; IRGN; steroids

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Post-streptococcal glomerulonephritis was once considered an innocuous self-limited disease of childhood. More recent literature has led to the understanding that IRGN in adults is not infrequent, and is associated with significant morbidity.¹ Since the pathogenesis of IRGN involves glomerular immune complex deposition along with complement activation, there has been an interest in the use of immunosuppressive therapy to modify the natural history of the disease. Existing data on the role of steroids have been scarce and observational.^{2–4} In this study, we report the results

of a randomized controlled trial that studied the effect of steroid therapy on renal outcomes in adults presenting with IRGN and a decreased estimated glomerular filtration rate.

METHODS

Trial Design

This was a single-center, open-label, parallel-arm, 1:1 randomized controlled trial conducted at the Institute of Nephrology, Madras Medical College. The trial was designed to compare corticosteroids added on to supportive care versus supportive care only, in the management of adults with IRGN and serum creatinine >1.5 mg/dl. Approval for the conduct of the trial was obtained from the Institutional Ethics Committee at the Madras Medical College. The trial was registered at the ISRCTN registry (ISRCTN13723530). There was no financial support for the trial.

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Participants

Patients were eligible for the trial if they were aged 18 years or older, had a serum creatinine >1.5 mg/dl at the time of randomization, and met at least 3 of the following 5 criteria for IRGN proposed by Nasr *et al.*:¹ (i) clinical or laboratory evidence of infection preceding or at the onset of glomerulonephritis, (ii) depressed serum complement, (iii) endocapillary proliferative and exudative glomerulonephritis, (iv) C3-dominant or codominant glomerular immunofluorescence staining, and (v) hump-shaped subepithelial deposits on electron microscopy. All patients underwent a percutaneous kidney biopsy prior to randomization.

Patients were excluded if more than 21 days had elapsed since the onset of kidney injury, or if they had contraindications for steroids, were seropositive for HIV, hepatitis B or hepatitis C, had persistent hypocomplementemia at 3 months, or if their biopsies showed crescents involving greater than 50% of the sampled glomeruli, diabetic nephropathy Renal Pathology Society class III or IV, or interstitial fibrosis and tubular atrophy of greater than 40%. All participants provided written informed consent.

Of note, patients who had active and ongoing infections were considered to have a contraindication to steroids, and were therefore not enrolled at presentation. Once the infection had been appropriately treated, such patients were eligible for randomization if less than 21 days had elapsed since the onset of kidney injury.

Randomization and Intervention

Patients were recruited from June 2017 to May 2020. Those with clinically active infection were first treated, whereas those without an obvious source were screened for ear, nose and throat, dental, and dermatological infections. They were then randomly assigned in a 1:1 ratio to receive either corticosteroids plus supportive care (intervention arm), or supportive care alone (control arm). Randomization was performed in blocks of 4 using a predetermined computer-generated list. Patients randomized to the intervention arm were given intravenous methylprednisolone, 1 g daily, for 3 consecutive days. This was followed by oral prednisolone 1 mg/kg per day for 1 month, followed by a slow taper at 5 mg/week. The control arm did not receive any placebo, and the trial was open-label. All patients received renal replacement therapy when deemed appropriate, and other supportive measures at the discretion of the treating clinician.

Trial Outcomes

Complete renal recovery was defined as an estimated glomerular filtration rate of >60 ml/min per 1.73 m²,

assessed at 6 months after randomization. Partial renal recovery was defined as a serum creatinine lower than the peak creatinine at initial admission, but with an estimated glomerular filtration rate <60 ml/min per 1.73 m², assessed at 6 months after randomization. Glomerular filtration rate was estimated by the chronic kidney disease-EPI creatinine equation (2009), with race defined for all participants as “non-Black.” Persistent proteinuria was defined as urine protein-to-creatinine ratio greater than 0.5, or a urine albumin dipstick 2+ or more, at 6 months after randomization.

The primary outcome was complete renal recovery at 6 months. Additional secondary outcomes included combined complete and partial renal recovery at 6 months, death or end stage kidney disease at 6 months, resolution of proteinuria at 6 months, and dialysis independence at any point within 6 months of randomization among patients who had dialysis-requiring renal failure at presentation. Adverse events were recorded during monthly follow-up visits.

Statistical Analyses

Based on existing literature suggesting a complete renal recovery rate of 83.2% in IRGN,⁵ we calculated that the enrollment of 86 patients would provide 80% power to detect a between-group difference in the primary outcome of 20%, at a 2-sided significance level of 0.05. Assuming a 5% attrition rate, the target sample size was set at 91.

Categorical variables are expressed as percentages, parametric data as mean \pm SD, and non-parametric data as median (interquartile range). For missing data, the last observation was carried forward. With regard to the prespecified primary and secondary outcomes and the adverse events, statistical comparisons were made between the 2 groups using the χ^2 test and the Fisher's exact test. The analysis of the primary and secondary outcomes was performed on the intention-to-treat population. Nevertheless, as a sensitivity analysis, statistical tests were also performed on the per-protocol population.

All probabilities were 2-tailed, and the level of significance was set at 0.05. All analyses were performed using IBM SPSS Statistics Version 23.

RESULTS

Enrollment

From June 2017 through May 2020, a total of 198 patients had renal biopsies that included IRGN in the differential diagnosis. Of these, 52 patients underwent randomization. Though the intended sample size was not achieved, the trial was terminated prematurely because of the disruption to services caused by the COVID-19 pandemic.

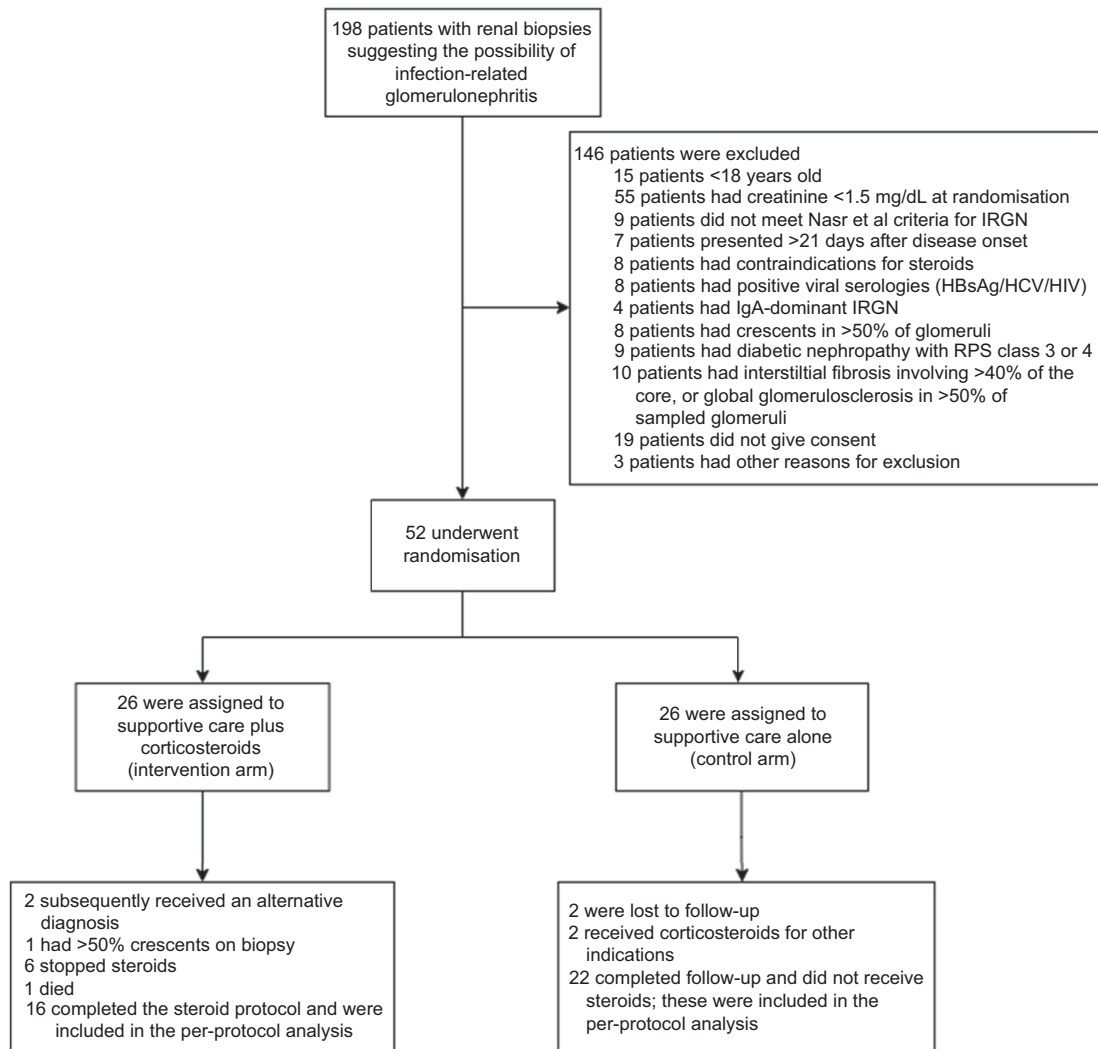


Figure 1. Description of participant flow in the trial. IRGN, infection-related glomerulonephritis; RPS, Renal Pathology Society.

Of the 52 patients, 26 were assigned to treatment with supportive care plus corticosteroids (intervention arm), and 26 to supportive care alone (control arm) (Figure 1). In the intervention arm, only 16 patients (61.5%) completed the steroid protocol and were included in the per-protocol analysis. Of the other 10 patients, 2 received alternative diagnoses (1 had C3 glomerulopathy on re-biopsy, and 1 developed crescentic glomerulonephritis on re-biopsy), 1 had >50% crescents on the original biopsy, 6 stopped steroids prematurely (4 due to infections), and 1 patient died 1 month after randomization. In the control arm, only 22 patients (84.6%) were included in the per-protocol analysis. Of the other 4 patients, 2 were lost to follow-up, and 2 received corticosteroids for other indications (1 for gout, and 1 for acute interstitial nephritis on re-biopsy).

Patients

Baseline characteristics are described in Table 1. More patients in the intervention arm had crescents on renal

biopsy; however, all other characteristics (including the peak serum creatinine and the presence of dialysis-requiring renal failure) were balanced between the 2 arms. The most common sources of infection were skin and soft tissue infections ($n = 23$) and dental caries ($n = 10$). Other identified sources of infection included

Table 1. Characteristics of the patients at baseline

Characteristic	Steroid arm ($n = 26$)	Non-steroid arm ($n = 26$)
Age (in yr)—mean \pm SD	42.8 \pm 14.9	43.3 \pm 13.4
Male sex—no. (%)	13 (50)	13 (50)
Diabetes mellitus—no. (%)	2 (7.7)	5 (19.2)
Hypertension—no. (%)	19 (73.1)	21 (80.8)
History of preceding or concurrent infection—no. (%)	19 (73.1)	20 (76.9)
Hypocomplementemia—no. (%)	15 (57.7)	15 (57.7)
Presence of crescents on biopsy—no. (%)	15 (57.7)	5 (19.2)
Presence of ATI on biopsy—no. (%)	15 (57.7)	14 (53.8)
Dialysis requirement at presentation—no. (%)	12 (46.2)	11 (42.3)
Peak serum creatinine—median (IQR) [in mg/dl]	4.5 (2.2-7)	3.35 (2.2-4.6)
Spot urine protein-creatinine ratio—median (IQR)	5.5 (3.6-7.6)	4.6 (1.9-8.8)

ATI, acute tubular injury; IQR, interquartile range; no., number.

Table 2. Primary outcome analysis in the intention-to-treat population

Primary outcome	Steroid arm [n/total (%)]	Non-steroid arm [n/total (%)]	Odds ratio (95% CI)	P value
Complete renal recovery at 6 mo	17/26 (65.4)	14/26 (53.8)	1.619 (0.530–4.946)	0.397

CI, confidence interval.

The primary outcome was complete renal recovery at 6 months after randomization, defined as an estimated glomerular filtration rate of >60 ml/min/1.73 m².

traumatic injury ($n = 3$), burn injury ($n = 1$), surgical site infection ($n = 1$), insect bite ($n = 1$), urinary tract infection ($n = 1$), upper respiratory infection ($n = 2$), lower respiratory infection ($n = 1$) and otomastoiditis ($n = 1$). Some individuals had more than one infectious focus.

Primary and Secondary Outcomes

At 6 months, there was no statistically significant difference between the number of patients achieving complete renal recovery in the steroid and non-steroid arms of the intention-to-treat population (17 of 26 patients [65.4%] vs. 14 of 26 patients [53.8%]; odds ratio 1.6; 95% confidence interval, 0.5–4.9; $P = 0.397$). None of the secondary outcomes were significantly different between the 2 groups in the intention-to-treat analysis. The results of all primary and secondary outcomes are presented in [Tables 2 and 3](#).

Analysis of the per-protocol population yielded similar results with regard to both the primary and secondary outcomes. These results are described in the Supplementary Material ([Supplementary Table S1 and S2](#)).

Adverse Events

Adverse events occurred significantly more often in the steroid arm than in the non-steroid arm (12 patients [46.2%] vs. 2 patients [7.7%]; odds ratio 10.3; 95% confidence interval, 2.0 to 52.8; $P = 0.002$) ([Table 4](#)). Infectious complications were the most frequent adverse event, with 7 infectious episodes noted in the steroid group, as compared with 2 in the control group. Infections included urinary tract infections ($n = 2$), soft tissue infections ($n = 3$), herpes zoster ($n = 2$), tinea corporis ($n = 1$), helminthiasis ($n = 1$). Other adverse events noted in patients who received steroids were Cushingoid facies ($n = 4$), hypokalemia ($n = 2$), gastrointestinal hemorrhage ($n = 1$), antral gastritis with bulbar duodenitis ($n = 1$), and new-onset diabetes ($n = 1$). One patient assigned to the steroid arm died

during the study period; there were no deaths in the control arm.

DISCUSSION

Despite significant strides made in our understanding of the pathogenesis of IRGN, there remains a lack of specific therapeutic interventions. Given that the disease is mediated by immune complex deposition in the glomerulus, it is intuitive that steroids might have a beneficial effect, a hypothesis that has so far not been tested in a clinical trial.

In a retrospective observational study of crescentic IRGN comprising 47 patients with >50% crescents on renal biopsy, the 78.7% of patients who received steroids were compared with the remainder who did not receive steroids. There was no significant difference in renal outcome between the 2 groups.⁶ Similar conclusions were drawn from an older study with a similar-sized cohort ($n = 52$).⁷ Nevertheless, multiple case reports^{4,8,9} and some observational data³ do suggest a potential benefit from steroids.

The current study was an open-label trial of steroids in adult patients with IRGN as defined by the Nasr *et al.*¹ criteria. This definition of IRGN was based on clinico-pathological criteria, highlighting another gap in our understanding of the disease, which is the lack of a specific biomarker. This necessarily meant that the studied population was heterogeneous, as evidenced by 2 patients who subsequently received a diagnosis of C3 glomerulopathy, and had to be retrospectively withdrawn from the per-protocol analysis.

The steroid protocol was based on consensus opinion and existing literature when the trial was designed.^{4,6} IgA-dominant IRGN was excluded because of concerns that its natural history and treatment response may be different from “classical” IRGN, particularly because of the association with active *Staphylococcal* infection.^{10,11} Similarly, patients with significant chronicity on renal biopsy were excluded because they would not be expected to have an optimal clinical response to steroids.¹²

Table 3. Secondary outcome analysis in the intention-to-treat population

Secondary outcomes	Steroid arm [n/total (%)]	Non-steroid arm [n/total (%)]	Odds ratio (95% CI)	P value
Combined CR/PR	22/26 (84.6%)	23/26 (88.5%)	0.717 (0.144–3.578)	0.685
Death/ESRD	4/26 (15.4%)	1/26 (3.8%)	4.545 (0.472–43.777)	0.350
Resolution of proteinuria	13/26 (50%)	12/26 (46.2%)	1.167 (0.393–3.466)	0.781
Dialysis independence	10/12 (83.3%)	10/11 (90.9%)	0.500 (0.039–6.439)	0.590

CI, confidence interval; CR, complete recovery; ESRD, end stage renal disease; PR, partial recovery.

Table 4. Adverse events reported during the study

Adverse events	Steroid arm [n = 26]	Non-steroid arm [n = 26]
Infectious events	7	2
Cosmetic side effects of steroids	4	-
Hypokalemia	2	-
GI side effects	2	-
New-onset diabetes	1	-
Death	1	-

GI, gastrointestinal.

The primary outcome was evaluated at 6 months after randomization. This short follow-up period was chosen because unlike chronic autoimmune conditions such as lupus nephritis, the glomerular inflammation in IRGN is expected to be self-limited once the infection is eradicated. Thus, any potential benefit of steroids would be demonstrable early, negating the need for longer-term follow-up, which might simply capture progressive chronic kidney disease after the initial insult from IRGN.

Adverse events, specifically infectious complications, were significantly higher in the intervention arm. Steroids were rapidly tapered and withdrawn in such patients, and all infections were treated successfully. Nevertheless, given the mounting evidence in both lupus nephritis and ANCA vasculitis that lower dose steroids are noninferior to the older higher-dose steroid protocols, it is acknowledged that the steroid dose used in our trial was likely far greater than required.

The major limitation of our trial is that it was a single-center study that did not achieve the target sample size because it was terminated prematurely on account of the COVID-19 pandemic. It is therefore possible that the lack of a significant difference in renal recovery between the 2 treatment arms may simply be a result of insufficient statistical power. Furthermore, it is not known whether certain specific subgroups of patients with IRGN, such as those with crescents on renal biopsy, or those who are dialysis-requiring at presentation, may benefit from steroids.

There was a chance assignment of a greater number of patients with crescents on renal biopsy to the steroid arm. Nevertheless, dialysis-requiring patients were equally distributed between the 2 arms, and the median peak serum creatinine level was also similar. This suggests that there was no difference in clinical severity between the groups.

Finally, though the triggering infectious syndrome was known, the specific microbiological agent was not identified for the patients in this study.

In this single-center trial, the use of corticosteroids did not increase rates of complete renal recovery at 6 months in patients with IRGN and serum creatinine

>1.5 mg/dl at presentation. There was an increased risk of adverse events with the use of corticosteroids.

DISCLOSURE

All the authors declared no competing interests.

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Data Availability Statement

Data available on request due to privacy/ethical restrictions

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Primary outcome analysis in the per-protocol population.

Table S2. Secondary outcome analysis in the per-protocol population.

CONSORT 2010 checklist of information to include when reporting a randomized trial.

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