Title: Tonsillectomy combined with steroid pulse therapy induces clinical remission of IgA nephropathy

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Abstract

Tonsillectomy combined with steroid pulse therapy has been a popular approach to treating IgA nephropathy (IgAN) in Japan for several years. However, little is understood about how such combined therapy affects the clinical course of IgAN. We therefore compared the effects of the combined therapy with those of steroid pulsing alone in a controlled study of patients with IgAN. The achievement ratio of clinical remission (CR), defined as the disappearance of urinary protein (UP) and occult blood (UOB), were compared between tonsillectomy combined with steroid pulse therapy (n = 35) and steroid pulse monotherapy (n = 20). The CR rate was higher in the group given combined therapy than monotherapy at the final observation 54.0 ± 21.2 months after the initial treatment (54.3 vs. 25.0%, p = 0.033). The Cox regression model showed that the combined therapy caused UP to disappear 6-fold more effectively than monotherapy. These findings suggest that tonsillectomy combined with steroid pulse therapy induces CR in patients with IgAN. Meanwhile, the indications for this therapy and verification of its positive long-term prognosis require urgent validation.

Body text

Tonsillectomy combined with steroid pulse therapy has received recent focus as a promising treatment for IgA nephropathy (IgAN) in Japan since Hotta et al. reported that about 60% of patients with IgAN treated in this manner achieved clinical remission (CR) defined as the disappearance of proteinuria and hematuria [1]. A nationwide

survey of the combined therapy in Japan also showed that 45.6% of 2,746 patients who received the combined therapy between 2000 and 2006, achieved CR after 12 months, but that patient selection, injected quantities of steroids and CR rates vary among institutions [2].

We therefore conducted a non-randomized controlled study to assess whether tonsillectomy combined with steroid pulse therapy causes CR more effectively than steroid pulse monotherapy among patients with IgAN [3]. Fifty-five patients were allocated to receive either combined therapy (n = 35) or monotherapy (n = 20), and repeated renal biopsies were obtained from 11 and 7 of the respective groups during the follow-up period. Both groups received intravenous methylprednisolone (0.5 g/day × 3 days), followed by oral prednisolone (initial dose, 0.5 mg/kg/day) for 12-18 months. The primary evaluation items were a 100% increase in serum creatinine (sCr) from baseline levels or the CR rate. Baseline clinicopathological data did not statistically differ between the groups given combined therapy or monotherapy (systolic blood pressure (SBP), 122.0 ± 12.9 vs. 127.6 ± 16.6 mmHg; UP, 1.06 ± 1.01 vs. 1.41 ± 1.05 g/day; sCr, 0.72 ± 0.29 vs. 0.84 ± 0.30 mg/dl). The CR rate was higher in the combined therapy than in the monotherapy group at 24 months after the initial treatment (61.8% vs. 17.6%; $p < 0.001$, χ^2 test), and the therapeutic effect persisted until the final observation at 54.0 ± 21.2 months (54.3% vs. 25.0%, $p = 0.033$, χ^2 test). None of combined therapy group achieved a 100% increase in sCr from the baseline level, whereas one patient in monotherapy group developed end-stage renal disease during the observation period. The histological findings of repeated biopsy specimens from 18 patients revealed significantly more reduced mesangial proliferation and IgA deposition

in the group that received combined therapy. The Cox regression model adjusted for known risk factors (SBP, UP, sCr, and histological severity) showed that the combined therapy was about 6-fold more effective in causing the disappearance of UP than steroid pulse monotherapy. These findings suggest that tonsillectomy combined with steroid pulse treatment induces clinical remission more effectively than steroid pulse monotherapy in patients with IgAN.

A possible mechanism for IgAN onset and progression has been proposed [4]. The initial phase is chronic antigenic stimulation of the innate immune system by the tonsillar mucosa via the "mucosa-bone marrow axis". Thereafter, aberrantly glycosylated IgA1 derived from the bone marrow is deposited within the mesangial area. Tonsillectomy might act "upstream" of the mechanism by eliminating antigenic stimuli from the tonsillar mucosa, whereas steroid pulse therapy acts "downstream" by suppressing the abnormal immune response in the bone marrow, which leads to subsequent inflammation in renal glomeruli. Thus, intervention against both pathogenic mechanisms might have a better therapeutic effect on IgAN than steroid monotherapy.

Our study however has several limitations. We used the surrogate markers of proteinuria and/or hematuria remission to assess renal outcome. Patients with advanced IgAN accompanied by sCr levels of > 2.0 mg/dl were excluded and the trial was not randomized. Other studies of the effectiveness of tonsillectomy combined with steroid pulse therapy have similar issues regarding study design, short follow-up periods, and lack of "true" end-points such as renal survival rates (Table 1). These Japanese studies also tended to select patients at the early phase of the disease, because Japan has an established annual health check-up system that monitors urinary parameters. In

consequence, the effectiveness of the combined therapy for patients with advanced IgAN remains unclear at this stage. Long-term and larger observational studies should assess the effectiveness of the combined therapy on actual renal outcome. A randomized controlled trial is ideal to establish a high level of evidence in the field, although tonsillectomy is a surgical procedure. Furthermore, validation of the indication for combined therapy based on tonsillar and renal findings is an important and urgent concern for otolaryngologists and nephrologists.

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Table 1. Effect of tonsillectomy combined with steroid pulse therapy on IgA nephropathy.

Author	Year	Study design	Patient type	No. of patients	Follow-up (months)	Treatment	End-point	Results
Hotta [1]	2001	Cohort	Adult	329	82	TSP vs. SP and/or OP	Clinical remission rate	Effect
Sato [5]	2003	Cohort	Adult	70	70	TSP vs. OP+/-CPA	Renal survival rate	No effect (sCr >2.0mg/dl)
Kawasaki [6]	2006	RCT	Child	32	37	TSP+WD vs. OP+WD+M	Clinicopathological data	Effect
Miyazaki [7]	2007	NRCT	Adult	101	60	TSP vs. SP vs. T	Clinical remission rate	Effect
Komatsu [3]	2008	NRCT	Adult	55	54	TSP vs. SP	Clinical remission rate	Effect
Kawaguchi [8]	2010	Cohort	Adult	388	24 (median)	TSP vs. SP vs. T	Clinical remission rate	Effect

RCT, randomized controlled trial; NRCT, non-randomized controlled trial; TSP, tonsillectomy combined with steroid pulse therapy; SP, steroid pulse therapy; OP, oral prednisolone; CPA, cyclophosphamide; W, warfarin; D, dipyridamole; M, mizoribine; T, tonsillectomy.