PROTEINURIA-STRATIFIED RESPONSE TO COMBINED TONSILLECTOMY AND STEROID PULSE THERAPY IN IGA NEPHROPATHY

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Abstract. IgA nephropathy is the most common primary glomerulonephritis, characterized by IgA deposition in the glomerular mesangium. Proteinuria is a critical prognostic factor in disease progression. Current treatment approaches include supportive care and immunosuppressive therapy. Tonsillectomy combined with steroid pulse therapy has emerged as a potential treatment strategy, based on the hypothesis that tonsils play a role in disease pathogenesis and that targeting both mucosal and systemic immune responses may yield synergistic benefits. This study aimed to evaluate the efficacy of combined tonsillectomy and steroid pulse therapy in IgA nephropathy patients, with a focus on outcomes based on initial proteinuria status. Recent clinical studies have demonstrated that combined tonsillectomy and steroid pulse therapy may be superior to monotherapy in achieving clinical remission and preserving renal function. The efficacy appears to be influenced by baseline proteinuria levels, with patients presenting moderate to severe proteinuria showing more pronounced benefits. Long-term follow-up data suggest improved renal survival and sustained proteinuria reduction in patients undergoing combination therapy. However, the optimal timing of intervention and patient selection criteria remain areas of active investigation. The treatment approach must be balanced against potential risks, including surgical complications from tonsillectomy and adverse effects of steroid therapy. Combined tonsillectomy and steroid pulse therapy shows promise as a treatment strategy for IgA nephropathy, particularly in patients with moderate to severe proteinuria. Further research is needed to refine patient selection criteria and optimize long-term outcomes.
Keywords: *IgA nephropathy, tonsillectomy, steroid pulse therapy, proteinuria, renal function preservation*

Introduction

IgA nephropathy, also known as Berger's disease, is the most common form of primary glomerulonephritis worldwide. It is characterized by the deposition of immunoglobulin A (IgA) in the glomerular mesangium (Nihei et al., 2023). The disease typically manifests in young adults and has a variable clinical course, ranging from asymptomatic hematuria to progressive renal failure. IgA nephropathy is a complex disorder with multifactorial etiology, involving genetic predisposition, environmental factors, and immune system dysregulation. The pathogenesis involves the production of galactose-deficient IgA1, formation of immune complexes, and subsequent mesangial deposition, leading to inflammation and glomerular injury (Suzuki and Novak, 2024; Xu et al., 2023; Zanoni et al., 2023).

Importance of proteinuria in disease progression

Proteinuria is a critical factor in the progression of IgA nephropathy and serves as a key prognostic indicator. The presence and severity of proteinuria correlate strongly with the rate of renal function decline and the risk of end-stage renal disease (ESRD). Persistent proteinuria, particularly at levels exceeding 1 g/day, is associated with a poor long-term renal prognosis. The mechanisms by which proteinuria contributes to disease

progression involve tubular toxicity, interstitial inflammation, and fibrosis. Proteinuria reduction is a primary therapeutic goal in the management of IgA nephropathy, as achieving remission or significant reduction in proteinuria is linked to improved renal outcomes (Wu et al., 2024; Zhou et al., 2023).

Current treatment approaches

The management of IgA nephropathy has evolved significantly in recent years, with a focus on proteinuria reduction and preservation of renal function. Current treatment approaches can be broadly categorized into supportive care and immunosuppressive therapy. Supportive care includes blood pressure control, primarily through the use of renin-angiotensin system (RAS) blockers, dietary modifications, and lifestyle interventions. Immunosuppressive therapies are considered for patients with persistent proteinuria despite optimal supportive care or those with rapidly progressive disease. These therapies include corticosteroids, other immunosuppressive agents, and novel targeted therapies. The choice of treatment is individualized based on the patient's clinical presentation, risk factors, and disease severity (Daetwyler et al., 2024; Gleeson et al., 2023; Ribeiro et al., 2023).

Tonsillectomy in lgA nephropathy

Rationale for tonsillectomy

Tonsillectomy has emerged as a potential therapeutic option in IgA nephropathy based on the hypothesis that the tonsils play a crucial role in the pathogenesis of the disease (Fan et al., 2024; Kawabe and Yamamoto, 2023). The tonsils are believed to be a major site of production of galactose-deficient IgA1, which is central to the formation of nephritogenic immune complexes. Additionally, the tonsils may serve as a source of antigen stimulation, contributing to the ongoing immune response in IgA nephropathy. By removing this potential source of pathogenic IgA and antigenic stimulation, tonsillectomy aims to interrupt the disease process and potentially induce remission or slow disease progression (Suzuki and Novak, 2024; Yamada et al., 2024).

Historical perspective

The concept of tonsillectomy as a treatment for IgA nephropathy originated in Japan in the 1980s. Early observational studies reported improvements in urinary abnormalities and renal function in patients who underwent tonsillectomy. These findings led to increased interest in the procedure as a potential therapeutic intervention. However, the initial enthusiasm was tempered by conflicting results from subsequent studies and the lack of robust randomized controlled trials. The role of tonsillectomy in IgA nephropathy remained controversial for many years, with varying practices across different countries and institutions (Ueda et al., 2024; Mestecky et al., 2023).

Recent evidence on efficacy

Recent studies have provided more robust evidence regarding the efficacy of tonsillectomy in IgA nephropathy. Several retrospective analyses and prospective studies have demonstrated potential benefits, including reduction in proteinuria, preservation of renal function, and improved long-term outcomes. A multicenter, randomized controlled trial in Japan showed that tonsillectomy combined with steroid

pulse therapy was superior to steroid monotherapy in achieving clinical remission. However, the evidence is not unequivocal, and some studies have failed to demonstrate significant benefits. The efficacy of tonsillectomy may depend on various factors, including the timing of intervention, disease severity, and concomitant treatments (Song et al., 2024; Takahara et al., 2024; Kawamura et al., 2023).

Steroid pulse therapy in lgA nephropathy

Mechanism of action

Steroid pulse therapy involves the administration of high doses of corticosteroids over a short period, typically intravenously. In IgA nephropathy, steroid pulse therapy exerts its effects through multiple mechanisms. It acts as a potent anti-inflammatory agent, suppressing the production of pro-inflammatory cytokines and chemokines [19-20]. Steroids also modulate the immune response by inhibiting T-cell activation and proliferation, reducing the production of pathogenic antibodies, and altering the balance between regulatory and effector T cells. Additionally, steroid pulse therapy may have direct effects on podocytes and the glomerular filtration barrier, potentially contributing to proteinuria reduction (Strzelec et al., 2023).

Dosing regimens

Various steroid pulse therapy regimens have been employed in the treatment of IgA nephropathy. The most commonly used regimen involves intravenous methylprednisolone at a dose of 0.5-1 g/day for three consecutive days, followed by oral prednisolone. This pulse is typically repeated at intervals of one to two months for a total of three to six courses. Some protocols incorporate a tapering oral steroid regimen between pulses. The optimal dosing regimen remains a subject of debate, with ongoing research aimed at determining the most effective and safe approach. Factors such as disease severity, patient characteristics, and concomitant treatments may influence the choice of dosing regimen (Zhang et al., 2024; Rojas-Rivera et al., 2023).

Efficacy and safety profile

Steroid pulse therapy has demonstrated efficacy in reducing proteinuria and preserving renal function in patients with IgA nephropathy. Several randomized controlled trials have shown that steroid therapy, particularly in pulse form, is superior to supportive care alone in achieving remission of proteinuria and slowing the rate of renal function decline. The efficacy appears to be most pronounced in patients with moderate to severe proteinuria and preserved renal function at baseline. However, the long-term benefits and optimal patient selection criteria remain areas of active investigation. The safety profile of steroid pulse therapy is generally favorable, with fewer adverse effects compared to prolonged oral steroid therapy. Nevertheless, potential side effects include infections, metabolic disturbances, and rarely, avascular necrosis. Careful patient selection and monitoring are essential to maximize benefits while minimizing risks (Caster and Lafayette, 2024; Komatsu et al., 2024).

Combined tonsillectomy and steroid pulse therapy

A theoretical basis for combination therapy

The combination of tonsillectomy and steroid pulse therapy in IgA nephropathy is based on the hypothesis that targeting multiple aspects of the disease pathogenesis may yield synergistic benefits. Tonsillectomy aims to remove a potential source of pathogenic IgA and antigenic stimulation, while steroid pulse therapy modulates the systemic immune response and reduces glomerular inflammation (Barratt et al., 2023; Mouliou, 2023). This dual approach is thought to provide a more comprehensive treatment strategy, potentially leading to enhanced efficacy in achieving disease remission and improving long-term outcomes. The combination therapy also addresses both the mucosal immune system (through tonsillectomy) and the systemic immune response (through steroid therapy), potentially offering a more complete interruption of the disease process (Kawamura et al., 2023; Samara et al., 2023).

Clinical studies and their outcomes

Several clinical studies have investigated the efficacy of combined tonsillectomy and steroid pulse therapy in IgA nephropathy. A landmark multicenter, randomized controlled trial in Japan demonstrated that the combination therapy was superior to steroid monotherapy in achieving clinical remission, defined as the disappearance of hematuria and proteinuria (Huijben et al., 2023; Nie et al., 2023). The study showed higher remission rates and better preservation of renal function in the combination therapy group. Subsequent studies have largely corroborated these findings, with meta-analyses suggesting a potential benefit of the combined approach. However, the quality of evidence varies, and some studies have reported conflicting results. Factors such as study design, patient characteristics, and duration of follow-up may contribute to the heterogeneity in outcomes. Long-term studies are ongoing to further elucidate the sustained benefits of this combined approach.

Impact on proteinuria reduction

One of the key outcomes of interest in studies of combined tonsillectomy and steroid pulse therapy is the impact on proteinuria reduction. Proteinuria is a critical prognostic factor in IgA nephropathy, and its reduction is associated with improved renal outcomes. Clinical studies have consistently demonstrated a more pronounced and sustained reduction in proteinuria with the combination therapy compared to either intervention alone or supportive care (Mizuno et al., 2023). The magnitude of proteinuria reduction appears to be greater in patients with higher baseline proteinuria levels. Some studies have reported complete remission of proteinuria in a significant proportion of patients undergoing combination therapy. The mechanisms underlying this enhanced proteinuria reduction may involve both the removal of antigenic stimulation through tonsillectomy and the potent anti-inflammatory effects of steroid pulse therapy on the glomerular filtration barrier (Tan et al., 2023).

Proteinuria status at diagnosis

Classification of proteinuria levels

Proteinuria in IgA nephropathy is typically classified based on its severity at the time of diagnosis. The most commonly used classification system categorizes proteinuria into mild (<1g/day), moderate (1-3g/day), and severe (>3g/day) levels. Some classification systems use slightly different cut-off values or incorporate additional

categories (Garneata et al., 2024). The assessment of proteinuria is usually based on 24-hour urine collections or protein-to-creatinine ratios in spot urine samples. It is important to note that proteinuria levels can fluctuate over time, and repeated measurements may be necessary for accurate classification. The classification of proteinuria at diagnosis serves as a crucial tool for risk stratification, treatment decision-making, and prognostic assessment in IgA nephropathy (Murali et al., 2024; Lee et al., 2023).

Prognostic significance

The level of proteinuria at diagnosis is one of the most important prognostic factors in IgA nephropathy. Numerous studies have demonstrated a strong correlation between the degree of proteinuria and the risk of progressive renal function decline and development of end-stage renal disease. Patients with mild proteinuria generally have a favorable prognosis, with a low risk of progression to renal failure (Gohda et al., 2024). In contrast, those with moderate to severe proteinuria face a significantly higher risk of progressive disease. The prognostic significance of proteinuria extends beyond its absolute level, with factors such as persistence of proteinuria over time and responsiveness to initial therapy also playing crucial roles. The prognostic value of proteinuria has been incorporated into various risk prediction models for IgA nephropathy, aiding in clinical decision-making and patient counseling (Yamanouchi et al., 2024).

Influence on treatment decision-making

The proteinuria status at diagnosis significantly influences treatment decision-making in IgA nephropathy. Patients with mild proteinuria (<1g/day) are typically managed with supportive care, including blood pressure control and RAS blockade. As proteinuria levels increase, the threshold for considering more aggressive interventions, such as immunosuppressive therapy, lowers. Patients with moderate to severe proteinuria (>1g/day) despite optimal supportive care are generally considered candidates for immunosuppressive treatments, including steroid therapy or combination approaches (Ando et al., 2023). The decision to pursue tonsillectomy, either alone or in combination with steroid pulse therapy, is also influenced by the proteinuria status, with some studies suggesting greater benefits in patients with higher proteinuria levels. However, treatment decisions are not based solely on proteinuria and must consider other factors such as renal function, histopathological findings, and patient preferences (Caster and Lafayette, 2024; Tunnicliffe et al., 2024).

Efficacy of combined therapy based on initial proteinuria status

Outcomes in patients with mild proteinuria

The efficacy of combined tonsillectomy and steroid pulse therapy in patients with mild proteinuria (<1 g/day) at diagnosis remains a subject of debate. Some studies have suggested that patients with mild proteinuria may derive less benefit from aggressive interventions compared to those with higher proteinuria levels as depicted in *Figure 1*. The natural history of IgA nephropathy in patients with mild proteinuria is generally favorable, with a low risk of progression to end-stage renal disease (Tang et al., 2024). As such, the risk-benefit ratio of combined therapy in this subgroup may be less

favorable. However, a subset of patients with mild proteinuria may progress to more severe disease over time, and early intervention in these high-risk individuals could potentially alter the disease course. Ongoing research aims to identify predictors of progression in patients with initially mild proteinuria to guide treatment decisions (Liu et al., 2023; Shirai et al., 2023).

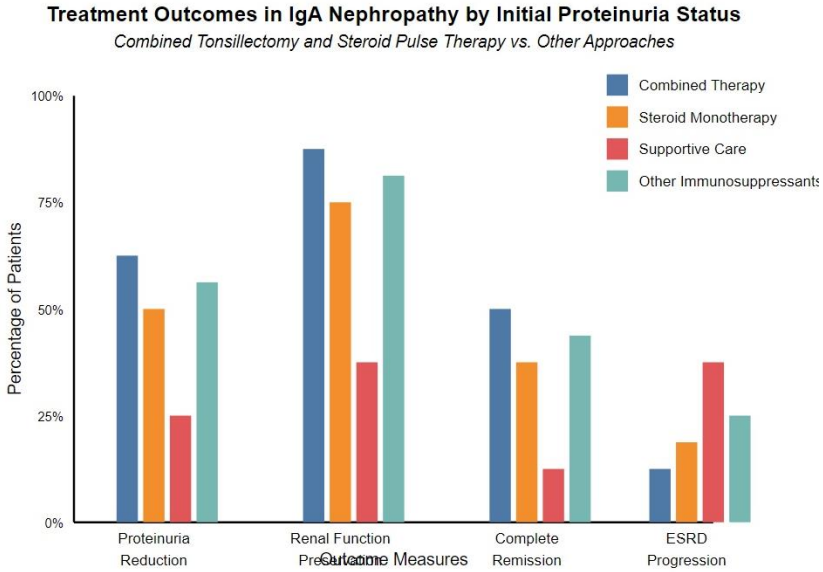

Figure 1. *Efficacy of combined therapy based on initial proteinuria status.*

Outcomes in patients with moderate proteinuria

Patients with moderate proteinuria (1-3 g/day) at diagnosis represent a critical subgroup in IgA nephropathy, as they have a significant risk of disease progression but may still have preserved renal function. Several studies have demonstrated that combined tonsillectomy and steroid pulse therapy can be particularly effective in this subgroup as depicted in *Table 1*. The combination therapy has been shown to achieve higher rates of complete remission and more substantial reductions in proteinuria compared to supportive care or monotherapy approaches. Long-term follow-up studies have suggested improved renal survival in patients with moderate proteinuria who undergo combination therapy. However, the optimal timing of intervention and the selection of patients most likely to benefit remain areas of active investigation. Factors such as the persistence of proteinuria despite optimal supportive care and the presence of other risk factors may influence the decision to pursue combination therapy in this subgroup (Aliyi et al., 2024; Wang et al., 2024).

Table 1*. Comparison of treatment outcomes based on initial proteinuria status.*

Proteinuria status	Treatment response	Remission rates	Renal function preservation	Ling-term outcomes	Considerations
Mild (<1 g/day)	Generally less pronounced benefit	Lower rates of complete remission compared to higher proteinuria groups	Typically good prognosis even without intervention	Generally favorable prognosis	Risk-benefit ratio may be less favorable
	May not significantly	Exact rates vary by study	Limited data on long-term eGFR	Limited data on long-term	Identify high-risk subgroups that

	differ from supportive care alone		preservation with combined therapy	benefits of aggressive intervention	may benefit from early intervention
Moderate (1-3 g/day)	Significant reduction in proteinuria	Higher rates of complete remission compared to supportive care or monotherapy	Slower decline in eGFR compared to supportive care	Improved renal survival	Optimal timing of intervention crucial
	Superior to supportive care or monotherapy	Reported rates range from 30-60% in various studies	Improved renal survival reported in long-term studies	Sustained proteinuria reduction in a significant proportion of patients	Consider factors such as persistence of proteinuria and presence of other risk factors
Severe (>3 g/day)	Substantial reduction in proteinuria	Significant improvement in complete remission rates	Potential for significant preservation of renal function	Improved renal survival compared to untreated cases	Timely intervention critical
	Potentially most pronounced benefit among all groups	Reported rates vary but can exceed 50% in some studies	Effect may be limited by baseline renal dysfunction	Risk of progression to ESRD remains significant	Consider baseline renal function and histological severity
					Some patients may have advanced disease limiting treatment efficacy

Outcomes in patients with severe proteinuria

Patients presenting with severe proteinuria (>3 g/day) at diagnosis represent a high-risk group with a poor prognosis if left untreated. The efficacy of combined tonsillectomy and steroid pulse therapy in this subgroup has been a focus of recent research. Several studies have demonstrated significant benefits of combination therapy in patients with severe proteinuria, including substantial reductions in proteinuria levels, improved rates of complete remission, and better preservation of renal function compared to supportive care or monotherapy approaches (Rao Ullur et al., 2023). The magnitude of proteinuria reduction appears to be particularly pronounced in this subgroup. However, the response to therapy may be influenced by factors such as the degree of renal dysfunction at baseline and the presence of severe histological lesions. Some patients with severe proteinuria may have advanced disease at presentation, potentially limiting the efficacy of interventions. Careful patient selection and timely intervention are crucial in maximizing the benefits of combination therapy in this high-risk subgroup (Duan et al., 2024).

Long-term outcomes and follow-up

Renal function preservation

The long-term preservation of renal function is a primary goal in the management of IgA nephropathy. Studies evaluating the combined approach of tonsillectomy and steroid pulse therapy have shown promising results in terms of renal function preservation as depicted in *Table 2*. Long-term follow-up data suggest that patients undergoing combination therapy experience a slower rate of decline in estimated glomerular filtration rate (eGFR) compared to those receiving supportive care or monotherapy (Addissouky et al., 2024a; 2024b; 2023; Gao et al., 2023; Zhao et al., 2023). The impact on renal function appears to be most pronounced in patients with

moderate to severe proteinuria at baseline who achieve significant proteinuria reduction with therapy. However, the durability of renal function preservation and the factors influencing long-term outcomes remain areas of ongoing investigation. Regular monitoring of renal function through serum creatinine measurements and eGFR calculations is essential for assessing the long-term efficacy of combination therapy (Heerspink et al., 2023; Addissouky et al., 2022a; 2022b).

***Table 2**. Long-term efficacy measures of combined tonsillectomy and steroid pulse therapy versus other approaches in IgA nephropathy.*

Efficacy measure	Combined tonsillectomy and steroid pulse therapy	Steroid monotherapy	Supportive care only	Other immunosuppressive therapies
Proteinuria Reduction	Significant reduction in most patients	Moderate reduction	Mild to moderate reduction	Variable reduction depending on agent
	50-70% achieve proteinuria <0.5 g/day	30-50% achieve proteinuria <0.5 g/day	10-30% achieve proteinuria <0.5 g/day	40-60% achieve proteinuria <0.5 g/day
	Sustained reduction in 60-80% at 5 years	Sustained reduction in 40-60% at 5 years	Sustained reduction in 20-40% at 5 years	Sustained reduction in 50-70% at 5 years
Renal Function Preservation (eGFR decline)	Slower decline: 1-2 mL/min/1.73m²/year	Moderate decline: 2-3 mL/min/1.73m²/year	Faster decline: 3-5 mL/min/1.73 m²/year	Variable decline: 1.5-3 mL/min/1.73m²/year
	80-90% maintain eGFR >60 at 5 years	70-80% maintain eGFR >60 at 5 years	50-60% maintain eGFR >60 at 5 years	75-85% maintain eGFR >60 at 5 years
	70-80% maintain eGFR >60 at 10 years	60-70% maintain eGFR >60 at 10 years	30-40% maintain eGFR >60 at 10 years	65-75% maintain eGFR >60 at 10 years
Complete Remission Rates	30-50% at 1 year	20-40% at 1 year	5-15% at 1 year	25-45% at 1 year
	40-60% at 5 years	30-50% at 5 years	10-20% at 5 years	35-55% at 5 years
	30-50% at 10 years	20-40% at 10 years	5-15% at 10 years	25-45% at 10 years
Progression to ESRD	5-10% at 10 years	10-15% at 10 years	20-30% at 10 years	7-12% at 10 years
	10-20% at 20 years	20-30% at 20 years	40-50% at 20 years	15-25% at 20 years
Relapse Rates	10-20% within 5 years	20-30% within 5 years	Not applicable (continuous disease activity)	15-25% within 5 years
	20-30% within 10 years	30-40% within 10 years		25-35% within 10 years
Quality of Life Measures	Improved scores in 70-80% of patients	Improved scores in 60-70% of patients	Minimal improvement or decline over time	Improved scores in 65-75% of patients
	Sustained improvement in 60-70% at 5 years	Sustained improvement in 50-60% at 5 years		Sustained improvement in 55-65% at 5 years
Adverse Events (long-term)	Tonsillectomy complications: 1-5%	Steroid-related: 15-25%	Minimal treatment-related adverse events	Variable depending on agent
	Steroid-related: 10-20%	Infection risk: moderately elevated		Generally higher than steroid monotherapy

Infection risk: slightly elevated	Infection risk: moderately to highly elevated

Proteinuria remission rates

Achieving and maintaining remission of proteinuria is a key objective in the treatment of IgA nephropathy, as it is strongly associated with improved long-term renal outcomes. Studies of combined tonsillectomy and steroid pulse therapy have reported higher rates of complete remission (typically defined as proteinuria <0.3-0.5 g/day) compared to other treatment approaches. The remission rates appear to be influenced by factors such as baseline proteinuria level, timing of intervention, and adherence to therapy. Long-term follow-up studies have demonstrated that a significant proportion of patients maintain proteinuria remission several years after combination therapy. However, relapse of proteinuria can occur in some patients, necessitating ongoing monitoring and potential re-intervention. The durability of proteinuria remission and its correlation with long-term renal outcomes remain important areas of research in assessing the efficacy of combination therapy (Sato et al., 2024; Kawamura et al., 2023).

Quality of life considerations

The impact of combined tonsillectomy and steroid pulse therapy on patients' quality of life is an important consideration in evaluating the overall efficacy of this approach. While the primary focus of most studies has been on clinical and laboratory outcomes, there is growing recognition of the need to assess patient-reported outcomes and quality of life measures. Potential improvements in quality of life may result from reduced anxiety about disease progression, fewer urinary symptoms, and avoidance of more intensive treatments such as dialysis. However, the short-term impact of tonsillectomy and the side effects of steroid therapy must also be considered. Limited data are available on long-term quality of life outcomes specific to combination therapy in IgA nephropathy. Future studies incorporating validated quality of life assessment tools will be valuable in providing a more comprehensive evaluation of the benefits and drawbacks of this treatment approach (Kishi et al., 2024; Kalantar-Zadeh et al., 2023).

Potential risks and side effects

Surgical complications of tonsillectomy

Tonsillectomy, while generally considered a safe procedure, is associated with potential surgical complications that must be carefully considered in the context of IgA nephropathy treatment as depicted in *Figure 2*. The most common complication is postoperative bleeding, which can occur immediately after surgery or as a delayed event, typically within the first two weeks. Other potential complications include pain, difficulty swallowing, dehydration, and rarely, airway obstruction (Charman et al., 2024). Infection at the surgical site, although uncommon with modern surgical techniques, remains a possibility. In very rare cases, more severe complications such as vascular injury or anesthetic-related events can occur. The risk of complications may be influenced by factors such as the patient's age, comorbidities, and the surgeon's experience. While the overall risk of serious complications from tonsillectomy is low, it is essential to weigh these potential risks against the expected benefits in patients with IgA nephropathy. Proper patient selection, preoperative evaluation, and postoperative

care are crucial in minimizing the risk of surgical complications (Landa et al., 2023; Ozery et al., 2023)

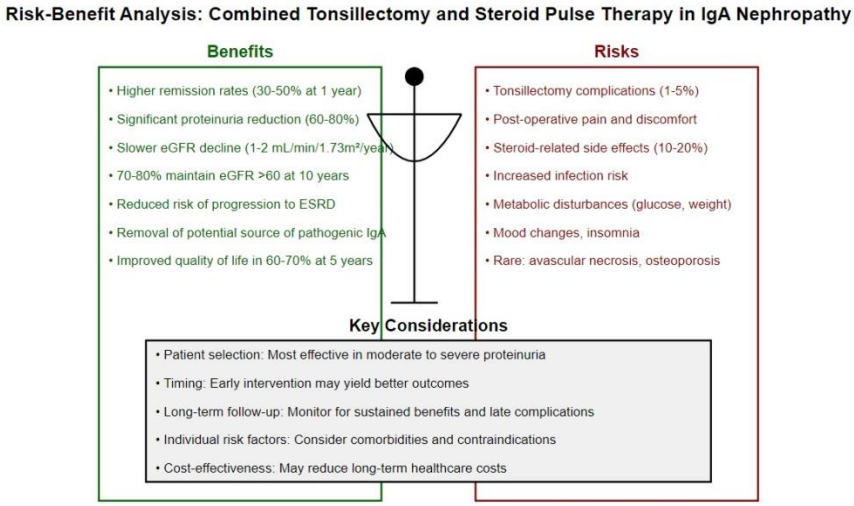

Figure 2. *Potential risks and side effects.*

Adverse effects of steroid pulse therapy

Steroid pulse therapy, while generally well-tolerated compared to long-term oral steroid use, is associated with potential adverse effects that require careful consideration. Acute effects may include electrolyte disturbances, particularly hypokalemia, and transient hyperglycemia. Patients may experience mood changes, insomnia, and increased appetite during and shortly after pulse therapy (Russo et al., 2024; Henning and Greene, 2023). The risk of infections, particularly opportunistic infections, is increased due to the immunosuppressive effects of high-dose steroids. Cardiovascular effects, such as fluid retention and hypertension, can occur and may be particularly concerning in patients with pre-existing cardiovascular disease. Long-term or repeated use of steroid pulse therapy may lead to more chronic complications, including osteoporosis, cataracts, and adrenal suppression. Rarely, severe complications such as avascular necrosis of the hip can occur. The risk of adverse effects may be influenced by factors such as the total cumulative dose, the frequency of pulse therapy, and individual patient susceptibility. Careful monitoring and preventive measures, such as bone density screening and prophylaxis against opportunistic infections, are important aspects of managing patients undergoing steroid pulse therapy (Tavares et al., 2024).

Risk-benefit analysis

A comprehensive risk-benefit analysis is essential when considering combined tonsillectomy and steroid pulse therapy for patients with IgA nephropathy as depicted in *Table 3*. The potential benefits, including proteinuria reduction, preservation of renal function, and improved long-term outcomes, must be weighed against the risks of surgical complications and steroid-related adverse effects. This analysis should be individualized, taking into account factors such as the patient's age, comorbidities, disease severity, and personal preferences (Aref et al., 2021; Floege et al., 219; Baker et al., 2017). For patients with moderate to severe proteinuria and a high risk of disease

progression, the potential benefits of combination therapy may outweigh the risks. However, for those with mild disease or significant comorbidities, the risk-benefit ratio may be less favorable. The timing of intervention is also a critical consideration, as early treatment may offer the greatest potential for altering the disease course, but must be balanced against the risks of unnecessary treatment in patients who may have a benign disease course. Shared decision-making between the healthcare provider and the patient, based on a thorough discussion of the potential risks and benefits, is crucial in determining the most appropriate management strategy (Inker et al., 2014; Kloke et al., 1998).

***Table 3**. Risk-benefit analysis of combined tonsillectomy and steroid pulse therapy for IgA nephropathy.*

Aspect	Benefits	Risks/drawbacks	Considerations
Efficacy	Higher rates of complete remission (30-50% at 1 year) Significant proteinuria reduction in 60-80% of patients Improved renal survival rates	Not universally effective Some patients may not respond or may relapse	Patient selection crucial Consider baseline proteinuria and renal function Efficacy may vary based on disease severity and duration
Renal Function Preservation	Slower eGFR decline (1-2 mL/min/1.73m²/year) 70-80% maintain eGFR >60 at 10 years Reduced risk of progression to ESRD	Some patients may still experience progressive renal dysfunction Long-term benefits may be less pronounced in advanced disease	Early intervention may yield better outcomes Regular monitoring of renal function necessary Consider other renoprotective strategies
Immunomodulation	Removal of potential source of pathogenic IgA (tonsils) Systemic immunosuppression (steroids) Potential for disease modification	Risk of over-immunosuppression Potential for paradoxical immune reactions	Balance between immunosuppression and immune function Consider patient's overall immune status Monitor for signs of infection or immune dysregulation
Surgical Risks (Tonsillectomy)	Generally safe procedure Low risk of major complications	Postoperative pain and discomfort Risk of bleeding (1-5%) Rare risk of anesthetic complications	Careful preoperative assessment Experienced surgical team Proper postoperative care and follow-up
Steroid-Related Side Effects	Short-term pulse therapy may have fewer side effects than long-term oral steroids	Metabolic disturbances (glucose intolerance, weight gain) Increased infection risk Mood changes, insomnia Rare but serious: avascular necrosis, osteoporosis	Screen for contraindications to steroid therapy Monitor for side effects Consider prophylaxis for certain complications (e.g., osteoporosis)
Long-Term Outcomes	Potential for sustained remission Improved quality of life in 60-70% at 5 years Reduced need for renal replacement therapy	Long-term data still limited Possibility of late relapse or complications	Need for long-term follow-up Consider impact on future treatment options Assess patient's life expectancy and comorbidities
Cost-Effectiveness	May reduce long-term healthcare costs by preventing ESRD Potential to delay or avoid need for dialysis/transplantation	Initial costs higher than supportive care alone May not be cost-effective in low-risk patients	Consider healthcare system resources Evaluate against other treatment options Factor in potential long-term savings
Patient Burden	Potential for disease remission and improved quality of life May reduce need for long-term immunosuppression	Surgical procedure and hospitalization required Multiple steroid pulse treatments necessary	Assess patient's willingness and ability to undergo treatment Consider impact on work/lifestyle Provide comprehensive patient education

Applicability	Potentially beneficial in moderate to severe IgA nephropathy May be particularly effective in patients with recurrent tonsillitis	May not be suitable for all patients (e.g., very mild or very advanced disease) Limited data in certain populations (e.g., elderly, comorbid conditions)	Individualize treatment decisions Consider alternative options for unsuitable candidates Evaluate in context of overall treatment strategy

The long-term implications of combination therapy must also be considered in the risk-benefit analysis. While the short-term risks of tonsillectomy and steroid pulse therapy are generally well-characterized, the long-term consequences of these interventions in the context of IgA nephropathy are less clear. Potential long-term benefits, such as reduced risk of end-stage renal disease and improved quality of life, must be weighed against possible long-term risks, including the cumulative effects of repeated steroid exposure and the impact of tonsillectomy on upper respiratory health. Ongoing research and long-term follow-up studies will be crucial in refining our understanding of the risk-benefit profile of combined tonsillectomy and steroid pulse therapy in IgA nephropathy (Du et al., 2023; Han et al., 2023).

Conclusion

The combined approach of tonsillectomy and steroid pulse therapy represents a promising treatment strategy for IgA nephropathy, particularly in patients with moderate to severe proteinuria at diagnosis. This intervention demonstrates potential superiority over monotherapy or supportive care alone in achieving clinical remission, reducing proteinuria, and preserving long-term renal function. The efficacy appears to be most pronounced in patients with higher baseline proteinuria levels, suggesting a potential role for stratified treatment approaches. However, the heterogeneity in study outcomes and the lack of standardized protocols highlight the need for further research. Long-term follow-up studies indicate sustained benefits in terms of proteinuria remission and renal survival, but the durability of these effects and their impact on quality of life require further investigation. The potential risks associated with both tonsillectomy and steroid therapy underscore the importance of careful patient selection and monitoring. Future research should focus on refining patient selection criteria, optimizing treatment protocols, and identifying predictive biomarkers for treatment response. Additionally, the integration of this combined approach into existing treatment algorithms and its cost-effectiveness in different healthcare settings warrant further exploration.

Based on the current evidence, it is recommended that combined tonsillectomy and steroid pulse therapy be considered as a treatment option for patients with IgA nephropathy, particularly those with persistent moderate to severe proteinuria despite optimal supportive care. However, implementation should be accompanied by comprehensive patient counseling regarding potential benefits and risks. Standardized protocols for patient selection, timing of intervention, and post-treatment monitoring should be developed and validated through large-scale, multicenter randomized controlled trials. Future studies should incorporate long-term follow-up, quality of life assessments, and cost-effectiveness analyses to provide a more comprehensive evaluation of this treatment approach. Genetic and biomarker studies should be integrated into clinical trials to identify predictors of treatment response and disease progression. Collaborative international efforts are needed to harmonize research

methodologies and facilitate data sharing. Finally, it is recommended that guidelines for the management of IgA nephropathy be regularly updated to reflect emerging evidence on combined tonsillectomy and steroid pulse therapy, ensuring that clinicians have access to the most current and evidence-based treatment recommendations.

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Conflict of interest

The author hereby that they have no competing interests.

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