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REVIEW

Mechanical versus Electronic Infusion Systems in Subcutaneous Immunoglobulin Therapy: A Structured Literature Review of Infusion-Site Reactions and Device Performance

Anna Majapuro-Hirvonen, Brent Rutland, Jasmin Bosshard

Global Clinical and Medical Affairs, KORU Medical Systems, Mahwah, NJ, USA

Correspondence: Anna Majapuro-Hirvonen, Global Clinical and Medical Affairs, KORU Medical Systems, 100 Corporate Drive, Mahwah, NJ, 07430, USA, Email amajapuro@korumedical.com

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Objective: Objective was to compare spring-driven mechanical and electronic infusion systems used for subcutaneous immunoglobulin (SCIg) therapy in patients with primary or secondary immunodeficiency (PID, SID) and chronic inflammatory demyelinating polyneuropathy (CIDP), with a focus on local infusion-site reactions and reliable dose delivery.

Methods: A structured literature review was conducted (PubMed, Cochrane Library, Google Scholar; January 26, 2026). Eligible studies reported safety outcomes. As direct measures of dose delivery were not consistently reported, infusion system performance was evaluated using pharmacodynamic response, with immunoglobulin G (IgG) levels at the end of the study period considered an indicator of successful dose delivery. Data were extracted and descriptively aggregated across studies. Risk of bias was appraised using validated tools appropriate to study design.

Results: Fourteen studies met the inclusion criteria (4 mechanical, 10 electronic). Mechanical infusion systems were associated with lower reported proportions of local infusion-site reactions, including swelling (23.1% vs 61.4%), redness (28.6% vs 44.0%), and soreness (22.9% vs 50.0%) compared with electronic infusion systems. Variability across studies was substantial, likely reflecting differences in patient populations, immunoglobulin formulations, infusion protocols, publication era, and outcome reporting methods. Across studies, both mechanical and electronic infusion systems achieved IgG levels consistent with therapeutic targets, supporting effective SCIg delivery.

Conclusion: Mechanical infusion systems were associated with consistently lower reported rates of local infusion-site reactions compared with electronic infusion systems in this descriptive synthesis, while both system types effectively achieved IgG levels consistent with adequate dose delivery. Although variability across studies warrants cautious interpretation, the overall pattern suggests a favorable tolerability profile for mechanical systems. Device selection should remain individualized, and further comparative research is warranted.

Keywords: drug delivery systems, infusion pumps, infusion site reaction, medical devices, subcutaneous immunoglobulin

Introduction

Subcutaneous immunoglobulin (SCIg) therapy is a key treatment modality for patients with primary or secondary immunodeficiency (PID, SID), and chronic demyelinating polyneuropathy (CIDP). Compared with intravenous immunoglobulin (IVIg), SCIg offers advantages such as reduced systemic adverse events[1] and greater patient autonomy due to home-based self-administration.

The method of delivery plays a critical role in treatment success, influencing safety, adherence, and quality of life.[2] This review provides a comparative evaluation of mechanical and electronic SCIg infusion systems, with emphasis on technical characteristics, safety, and performance outcomes.

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Background

Subcutaneous Immunoglobulin Replacement Therapy

Immunoglobulin replacement therapy (IgRT) is a cornerstone in the treatment of primary and secondary immunodeficiencies (PIDs and SIDs), as well as chronic inflammatory demyelinating polyneuropathy (CIDP). This therapy involves the administration of immunoglobulins to bolster the immune function and manage autoimmune processes. By supplying essential antibodies, IgRT helps reduce infections, control inflammation, and enhance immune system performance across a range of immune-mediated conditions.[3]

IgRT may be administered intravenously (IVIg) or subcutaneously (SCIg, including facilitated SCIg), depending on clinical indication, patient preference, tolerability, venous access, dosing needs, and site-of-care considerations. IVIg is commonly administered every 3−4 week, often in a hospital outpatient, infusion-centre, or supervised home-care setting. Infusion rates are typically increased stepwise according to tolerability; for example, prescribing information for IVIg describes an initial slow infusion period followed by gradual rate escalation, and patient guidance commonly describes IVIg sessions lasting approximately 2−4 hours, although longer infusions may be required depending on dose, medicinal product, tolerability, and local protocol.[4]

SCIg is generally used for long-term maintenance therapy[2] and is typically administered more frequently than IVIg, most commonly weekly, biweekly, or at individualized intervals. Because the monthly immunoglobulin dose is divided into smaller subcutaneous doses, SCIg is associated with more stable serum IgG concentrations, reduced peak-trough variation, avoidance of venous access, and fewer systemic infusion-related reactions compared with IVIg.[5,6] SCIg can often be self-administered at home after training, reducing the need for repeated hospital visits and supporting treatment flexibility and quality of life.

The volume of IgG administered subcutaneously varies by medicinal product concentration, indication, prescribed dose, patient weight, number of infusion sites, and local tolerability. Conventional SCIg products are commonly supplied as 16.5−20% IgG solutions. Product labeling illustrates the practical range of infusion volumes: for example, Hizentra® (20%) (immune globulin subcutaneous (human)) (CSL Behring LLC) allows subsequent infusion volumes up to 50 mL per site for adults; Cutaquig® (16.5%) (immune globulin subcutaneous (human) - hipp) (Octapharma AG), Cuvitru® (20%) (immune globulin subcutaneous (human)) (Takeda Pharmaceutical Company Limited), and Xembify® (20%) (immune globulin subcutaneous, human-klhw) (Grifols S.A.) allow up to 30 mL per site in prescribing information (PI). Facilitated SCIg, such as HyQvia® (10%) (immune globulin infusion, human, and recombinant human hyaluronidase) (Takeda Pharmaceutical Company Limited), enables larger less-frequent infusions, with typical dosing intervals of 3 −4 weeks and administration of the monthly dose in one or two sessions.[7] For example, a 70-kg patient prescribed SCIg at 0.4 g/kg/month would receive 28 g of immunoglobulin monthly, equivalent to approximately 140 mL of a 20% formulation. If administered weekly, this regimen would correspond to approximately 35 mL per infusion, distributed across one or more infusion sites according to product labeling, patient tolerability, and preference.

Administration of high-volume subcutaneous biologics such as SCIg can be performed manually or through various infusion systems. Commonly used systems include portable, battery-operated electronic infusion systems and mechanical spring-driven devices. Larger-scale electronic pumps and elastomeric systems are generally not used in home settings because of limitations in their technical capabilities, cost, or practicality.

For each SCIg administration, the subcutaneous needle set is inserted into the subcutaneous tissue and removed after completion of the infusion; the infusion site could be changed or rotated with each administration. Thus, the needle or soft subcutaneous cannula, together with the adhesive dressing securing it to the skin, is part of the system that has direct contact with the patient's skin during treatment. In contrast, the pump, syringe, flow rate tubing or other administration tubing remain external to the body. Across manual push, mechanical, and electronic SCIg delivery methods, the skin-contacting components are broadly similar, differences mainly in the needle tip design, because all require subcutaneous access via a needle or cannula set.

Manual Push Administration

The manual push technique entails the direct delivery of the medicinal product into the subcutaneous tissue using a syringe, tubing, and needle. This hands-on method allows patients or caregivers to control the infusion rate manually by

depressing the syringe plunger, making real-time adjustments based on patient feedback and comfort. This approach is cost-effective, requires minimal equipment, and is portable, making it particularly practical for home or travel use.

Manual push is particularly suitable for small-volume administrations and can be used when patients choose to split weekly doses into smaller and more frequent infusions.[2] It also requires minimal training, although patients with limited manual dexterity may find the technique to be challenging. Despite this, its simplicity and low cost make it a viable option for patients and healthcare providers.

Electronic Infusion Systems

Electronic infusion systems represent a more advanced method of subcutaneous administration, providing precise and consistent dosing over extended periods. These programmable, battery-operated infusion systems can deliver medicinal products at fixed or variable flow rates, offering customization to suit complex treatment regimens. One of the key advantages is the ability to maintain consistent flow rates despite fluctuations in tissue backpressure, ensuring accurate delivery, and reducing user error.

Programmability allows tailored infusion schedules, and portability supports patient autonomy and mobility during therapy. However, these benefits come with higher costs, for both the devices themselves and associated consumables such as batteries and potentially proprietary syringes. Additionally, electronic systems require adequate training for patients and caregivers to operate and troubleshoot safely.[8] Technical failures or malfunctions can interrupt treatment, requiring backup plans and potentially complicating home administration.

Although electronic infusion systems offer precision and automation, their complexity and cost may limit their suitability for some patients. Nonetheless, for individuals requiring consistent dosing or those who struggle with manual technique, they provide a valuable alternative.

Mechanical Infusion Systems

Mechanical infusion systems, particularly spring-driven devices, offer reliable and user-friendly solutions for SCIg administration. Some of these systems utilize a constant-force spring mechanism to deliver medicinal products at a steady flow rate. Their operation is straightforward: the user loads the syringe, connects the flow rate tubing and needle set, and activates the device. Mechanical infusion systems function without electronics or batteries, thereby minimizing the risk of device failure and reducing maintenance requirements.

In addition, mechanical devices are lightweight, portable, and generally less costly than electronic alternatives. They provide consistent medicinal product delivery through fixed or adjustable flow rate tubing, avoiding the complexity associated with programmable systems. While this method offers less dosing flexibility compared with electronic infusion systems, simplicity, durability, and ease of use of mechanical systems make them a practical and robust option for many patients requiring long-term subcutaneous therapies such as SCIg.

Technical Differences of Electronic and Mechanical Infusion Systems

The fundamental difference between electronic and mechanical infusion systems is their mechanisms of action. Electronic systems infuse medicinal products at a programmed rate and can dynamically adjust the output pressure to maintain the flow rate if the resistance at the infusion site increases. In contrast, mechanical systems exert constant pressure using a spring, which naturally decreases the flow rate in response to increased tissue pressure (Figure 1). This characteristic acts as a built-in safety feature by preventing over-infusion under backpressure conditions.

Examples of commonly used infusion systems for SCIg administration are listed in Table 1, which highlights their typical performance and safety features.

Optimizing SCIg Infusion Experience

Successful SCIg infusion depends on several interrelated factors, including patient selection, proper training, and adherence to the prescribed regimen.[1] A positive infusion experience is critical for maintaining long-term compliance and achieving optimal treatment outcomes. Key variables such as flow rate, infusion volume, needle length, and infusion pressure all influence patient comfort and the effectiveness of administration.

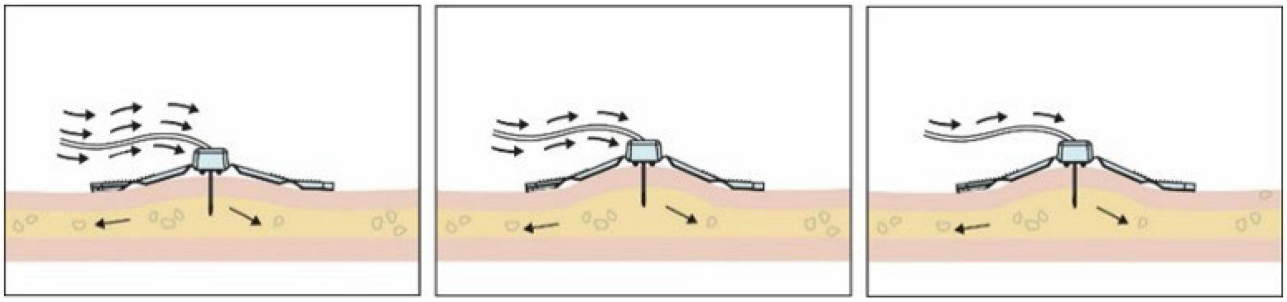

Figure 1 Schematic representation of constant-pressure delivery in mechanical infusion systems: flow rate decreases in response to increasing subcutaneous tissue resistance. Arrows above the skin indicate the relative infusion flow into the subcutaneous tissue. The progressive reduction in flow reflects increasing tissue resistance as fluid accumulates at the infusion site, helping to prevent tissue saturation, excessive local tissue distension, and infusion-site reactions.

PI for each medicinal product provides guidance to healthcare providers in determining appropriate infusion parameters, taking into account patient preferences, tolerability, and clinical requirements. Among these considerations, the pressure profile of the infusion system is often underrecognized. However, pressure dynamics during SCIg administration can significantly impact both safety and tolerability and therefore warrant careful consideration when selecting a device.

During SCIg administration, the subcutaneous tissue expands to accommodate the infused fluid,[9] and higher flow rates may lead to increased backpressure and mechanical strain,[12] as illustrated in Figure 2. Electronic infusion systems typically operate at a constant flow rate, increasing delivery pressure as needed to maintain that rate, which may result in discomfort when tissue resistance increases. In contrast, mechanical infusion systems operate at constant, low driving pressure, often generated by a spring mechanism, allowing the flow rate to decrease naturally as tissue resistance increases. This pressure-responsive behavior may help reduce site-related adverse events and improve patient comfort, underscoring the importance of considering the device-specific pressure dynamics in the selection of an infusion system.

Infusion System Safety and Performance Outcomes

The primary function of an infusion system is to deliver prescribed medicinal products subcutaneously for therapeutic use. A safe delivery includes the prevention or minimization of local infusion site reactions caused by an infusion system. Literature reports on a wide range of potentially occurring local reactions such as swelling, itching, redness, soreness, or bleeding. Other safety measures like air-in-line or fluid occlusions in the infusion systems could not be found in published literature.

Performance is commonly defined as the infusion system's effectiveness in administering the prescribed dose to the intended patient population, consistent with its intended use. Because clinical studies do not typically report direct

Table 1 Typical Performance and Safety Features of SCIg Administration Methods

SC Administration Method	Example Products	Performance Features	Safety Features
Manual Push	Standard syringe and SC needle	Variable pressure and flow rates; Direct user control	Dependent on user technique
Electronic Infusion System	Crono-family (Cané S.R.L).,[9] SoConnect+ (FDE),[10] Micropump MP, mlh+ Multi Syringe (Micrel)[11]	Constant or adjustable flow rates; programmable; battery-operated	Alarms; pressure sensors; air-in-line detection; user interface; optional data logging capability
Mechanical Infusion System	FreedomEdge, Freedom60 (KORU Medical Systems),[12] SCIg60 (EMED),[13] Insignis (IHS)[14]	Constant low pressure; fixed or adjustable flow rates; spring-driven mechanisms	Flow rate decreases with increasing tissue resistance; durable; low maintenance; ease of use

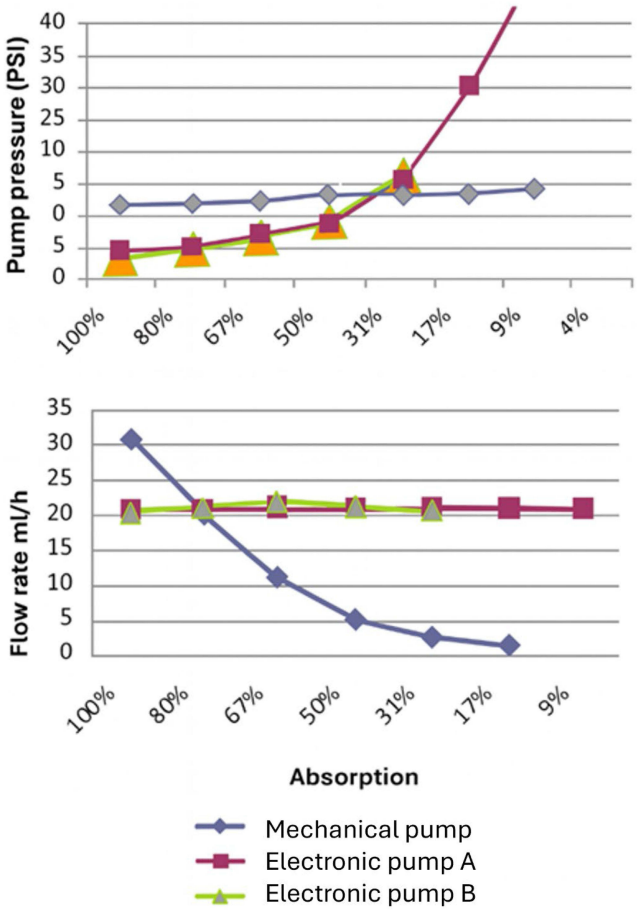

Figure 2 Schematic Representation of the Relationship Between Infusion Pressure, Flow Rate, and Subcutaneous Tissue Resistance During Subcutaneous Administration.

measures of dose delivery, performance outcomes can be evaluated based on pharmacodynamic response, as reflected by IgG levels measured at the end of a study period. In this study, this endpoint was considered an indicator of successful delivery of the full prescribed dose.

Immunoglobulin replacement therapy is typically initiated in patients with very low (<1.0 g/l) or significantly reduced (1.0−2.99 g/l) IgG levels and impaired antibody responses. Dosing and infusion frequency are individualized to maintain IgG levels above 6.0 g/l, with higher levels potentially associated with improved clinical outcomes.[10]

Methods

Review Design and Objectives

A structured literature review was conducted to compare the safety and performance outcomes associated with mechanical and electronic infusion systems used for SCIg administration. The review employed predefined eligibility criteria, a structured search strategy, independent study screening, and standardized data extraction procedures.

The primary objective of this study was to evaluate clinical data from published studies reporting safety outcomes related to local infusion-site reactions, including redness, swelling, and soreness. These outcomes were selected based on their consistent reporting across immunodeficiency studies, particularly those evaluating immunoglobulin therapies, and their relevance to patient experience, treatment adherence, and clinical decision-making.[11,13]

The review was designed using the Population, Intervention, Comparison, and Outcomes (PICO) framework. The target population included patients of all ages diagnosed with PID, SID, or CIDP. The intervention of interest was administration of SCIg via mechanical infusion systems, with electronic infusion systems serving as comparators. The

primary outcomes were local infusion-site reactions, and the secondary outcome was pharmacodynamic response, with end-of-study IgG levels used as an indicator of successful delivery of the prescribed dose.

Search Strategy

To ensure identification of studies in which the infusion device was clearly specified and where the study focus included the use of the medical device rather than solely the infused medicinal products, manufacturer and infusion device (pump) names were incorporated into the search strategy. Device-related keywords were selected based on the overview by Franzese et al[14] of commonly used devices for SCIg administration, as well as the author's therapeutic area expertise.

The search strategy combined terms for subcutaneous administration and immunoglobulin with device specific keywords as follows:

(subcutaneous OR SC) AND (immunoglobulin OR immune globulin OR IG) AND ("freedom60" *OR* "freedom 60" *OR* "freedomedge" *OR* "freedom edge" *OR* "EMED" *OR* "Innovative Health Sciences" *OR* "Graseby Medical" *OR* "CME T34L" *OR* "Medis Infusa T1" *OR* "Crono" *OR (*"CADD" *AND pump) OR* "So-Connect" *OR* "Eitan Medical" *OR* "Micrel").

The search strategy was adapted for each database as appropriate.

Searches were performed on January 26, 2026, in PubMed, the Cochrane Library, and Google Scholar.

Eligibility Criteria

Studies were eligible for inclusion if they met all of the following criteria:

1. Included patients with PID, SID, or CIDP receiving SCIg therapy;
2. Evaluated a mechanical or electronic infusion system identified by product and/or manufacturer name;
3. Reported safety and/or performance outcomes associated with SCIg administration;
4. Were published in peer-reviewed journals;
5. Included at least 10 patients; and
6. Provided sufficient methodological detail to allow objective assessment of outcomes.

Studies were excluded if they were non-clinical investigations (animal, cadaveric, bench-testing, or simulation studies), case reports, review articles, unrelated to SCIg infusion devices, involved off-label use, lacked ethical approval where applicable, were published in languages other than English, or failed to identify the infusion device used or report device-specific outcomes.

Study Selection

A total of 788 records were identified through database searching. After removal of 59 duplicates, 729 titles and abstracts were screened for relevance.

Two independent reviewers (AMH and JB) screened all titles and abstracts against predefined eligibility criteria. Potentially eligible studies underwent full-text review. Disagreements were resolved through discussion and consensus.

Following title and abstract screening, 688 records were excluded and 41 publications underwent full-text review. Fourteen studies met the inclusion criteria and were included in the final descriptive synthesis. The study selection process is summarized in Figure 3. No relevant studies were identified in the Cochrane Library.

Data Extraction and Synthesis

Data extraction was performed independently by two reviewers (AMH and JB) using a standardized data abstraction form developed before review initiation. Extracted variables included study design, patient characteristics, indication, infusion device type, outcome measures, infusion-site reactions, IgG levels, and reported safety outcomes. Any discrepancies were reviewed jointly and resolved by consensus.

Due to heterogeneity in study populations, infusion protocols, outcome definitions, and reporting methods, a formal pooled-effect meta-analysis was not performed. Instead, outcomes were synthesized descriptively. Local infusion-site

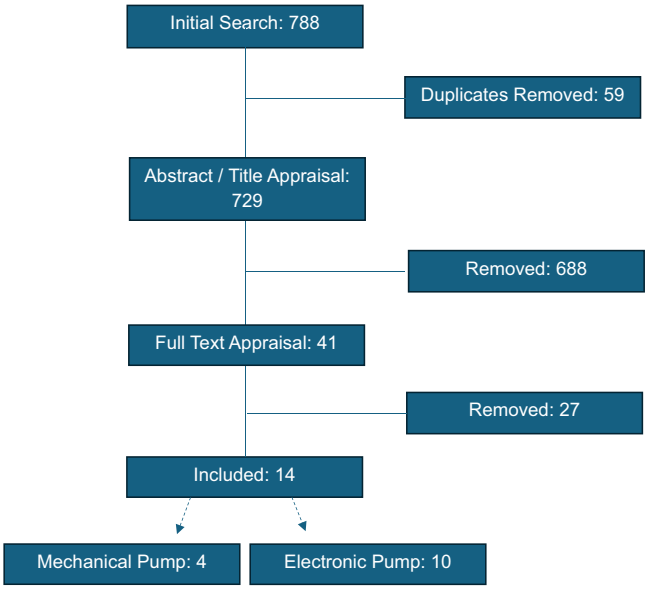

Figure 3 Flow Diagram for Study Selection.

reactions were summarized using aggregated patient-level data reported in the included studies. Treatment performance was assessed descriptively using reported end-of-study IgG levels.

Both reviewers had prior experience in literature review methodology, clinical research, and medical device evaluation.

Methodological Quality Assessment

The methodological quality of included studies was assessed in accordance with the principles outlined in Medical Device Coordination Group Document MDCG 2020−6[15] and the EU Medical Device Regulation (2017/745).[16]

Methodological quality and potential sources of bias were assessed qualitatively across key domains including randomization, blinding, presence of a comparator, sample size, handling of missing data, outcome measurement, and potential conflicts of interest.

Among studies evaluating mechanical infusion systems, one randomized crossover trial was identified, with some concerns related to rescue therapy and potential unblinding. The remaining studies were open-label, nonrandomized, and lacked comparators, resulting in overall high risk of bias (Table 2).

Studies evaluating electronic infusion systems were predominantly uncontrolled, open-label, or retrospective and frequently relied on patient-reported outcomes, selected populations, and industry funding. These characteristics contributed to a consistently high risk of bias (Table 3). A summary of the methodological quality assessment is provided in Figure 4.

Results

Study Characteristics

Fourteen (14) peer-reviewed studies reporting per-patient local infusion-site reactions met the inclusion criteria. Four (4) studies evaluated mechanical infusion systems and ten (10) evaluated electronic infusion systems.

Mechanical cohorts[17–20] (Table 2) evaluated the Freedom™ Infusion System, whereas comparator cohorts evaluated various electronic infusion systems[21–30] (Table 3). Device-specific search terms were used to identify studies reporting on infusion system characteristics and outcomes. One study evaluating an alternative mechanical infusion system was found but excluded due to lack of relevant clinical outcome data.

Table 2 Characteristics of Studies Evaluating Mechanical Infusion Systems for SCIg Administration

Citation	Level of Evidence	Risk of Bias	Study Devices	No. Patients	Study Design	Diagnoses	Age, Mean (Range)	Variables Provided
Katzberg 2016[17]	4	High: No control/ blinding; small sample; attrition; rescue dosing; partly subjective outcomes; industry funding/ conflicts	Freedom60 Infusion System	15	Prospective, open-label	MMN (multifocal motor neuropathy)	51.7 (31–82)	IgG levels; local infusion-site reactions; systemic symptoms; infusion time; demographics
Latysheva 2020[18]	4	High: Uncontrolled, open-label; subjective outcomes; no imputation; industry-funded with author conflicts	Freedom60 Infusion System	25	Prospective, Phase II study	PID (primary immunodeficiency)	Mean 35.2 (18–70)	IgG levels; infection rate; local infusion-site reactions; neurological symptoms; systemic symptoms; demographics
Markvardsen et al 2013[19]	4	Some concerns: Randomized, blinded; rescue therapy/ discontinuations; possible unblinding	Freedom60 Infusion System	30 (14 receiving SCIG)	Randomized crossover (SCIg vs saline following IVIg)	CIDP (chronic inflammatory demyelinating polyneuropathy)	53.4 (18–80)	IgG levels; local infusion-site reactions; demographics
Niebur et al 2015[20]	4	High: Uncontrolled, unblinded; dose increase confounds comparison; single-center; industry-funded with author conflicts	Freedom60 Infusion System	32	Prospective, open-label, single-center and single arm study	PID	14.5 (2–75)	IgG levels; infection rate; local infusion-site reactions; infusion time; demographics

Infusion-Site Reactions

Across studies, descriptively aggregated data indicated lower reported proportions of local infusion-site reactions with mechanical infusion systems compared with electronic systems.

Swelling was reported in 24 of 104 patients (23.1%; 95% CI, 15.3%−32.4%) in mechanical infusion system cohorts and in 205 of 334 patients (61.4%; 95% CI, 55.9%−66.8%) in electronic infusion system cohorts (Table 4).

Redness was reported in 34 of 119 (28.6%; 95% CI, 20.6%−37.6%) using the mechanical infusion system and in 147 of 334 patients (44.0%; 95% CI, 38.6%−49.5%) using electronic infusion systems (Table 5). Soreness was reported in 24 of 105 patients (22.9%; 95% CI, 15.2%−32.1%) using the mechanical infusion system and in 173 of 386 patients (50.0%; 95% CI, 44.6%−55.4%) using electronic infusion systems (Table 6).

Performance

Performance was evaluated using pharmacodynamic response, with IgG levels at study completion considered an indicator of successful dose delivery. Five studies reported IgG levels for mechanical infusion systems and six for electronic infusion systems.

Across studies, both mechanical and electronic infusion systems achieved IgG levels consistent with therapeutic targets. Descriptively, mean IgG levels tended to be higher in studies evaluating mechanical infusion systems (weighted mean 12.32 g/l) compared with electronic infusion systems (9.54 g/l), although cross-study differences in dosing regimens, baseline IgG levels, and patient populations limit direct comparability. Mean IgG levels shown in Figures 5 and 6.

Table 3 Characteristics of Studies Evaluating Electronic Infusion Systems for SCIg Administration

Citation	Level of Evidence	Risk of Bias	Study Devices	No. Patients	Study Design	Diagnoses	Age, mean (range)	Variables Provided
Abrahamsen et al 1996[21]	6	High: Uncontrolled, unblinded case series (n=8); retrospective review and caregiver-reported outcomes; subjective measures; no formal analysis	MS16A (Graseby Medical, UK)	8	Retrospective chart review and questionnaire	PID (primary immunodeficiency)	8 (4.5–12)	IgG levels; infection rate; local infusion-site reactions; demographics
Borte et al 2017[22]	6	Some concerns: Uncontrolled, open-label; reliance on patient-reported AEs; no comparator; industry-sponsored with author affiliations	CME T34L (Caesarea Medical Electronics, Caesarea, Israel)	49	Prospective, non-controlled clinical trial	PID	17 (median)	IgG levels; infection rate; local infusion-site reactions); demographics
Gardulf et al 1995[23]	6	High: Uncontrolled, nonrandomized; reliance on medical records and patient-reported data; subjective outcomes; variable reporting practices across sites	MS16A (Graseby Medical, UK)	165	Cohort study based on medical records and questionnaires	PID	43 (13–76)	IgG levels; local infusion-site reactions; demographics
Gardulf et al 1991[24]	6	High: Uncontrolled, open-label; no comparator; reliance on patient-reported outcomes; selected high-risk population; potential reporting bias	MS16A (Graseby Medical, UK)	25	Prospective clinical study	PID	43	IgG levels; infection rate; local infusion-site reactions
Gustafson et al 2008[25]	6	High: Uncontrolled, open-label; small sample; exclusion of higher-risk patients; reliance on patient-reported AEs; industry-sponsored with author conflicts	Infusa T1 (Medis S.R.L., Italy)	12	Prospective pharmacokinetic study	PID	62 (22–72), median	IgG levels; local infusion-site reactions
Hansen et al 2002[26]	6	High: Uncontrolled, open-label; preselected experienced patients; reliance on patient-reported outcomes; no blinding/comparator; some attrition	MS16A (Graseby Medical, UK)	50	Prospective study	PID	48 (23–74)	Local infusion-site reactions
Jolles et al 2011[27]	6	High: Uncontrolled, open-label; pretreated stable patients; reliance on patient-reported and AE outcomes; missing data not imputed; industry-sponsored with author affiliations	Crono PCA-50 or Super-PID (Cane S.R.L., Italy)	51	Prospective, open-label, multicenter, single-arm, Phase 3 study	PID	21.5	IgG levels; infection rate
Wasserman et al 2010[28]	6	High: Unblinded, single-arm crossover; no comparator; selected stable patients; partly subjective outcomes; missing data not described; industry funding with author affiliations	CADD-Legacy PLUS (Smiths Medical, USA)	32	Open-label, single sequence, crossover trial	PID	44 (13–68)	IgG levels; infection rate; local infusion-site reactions

(*Continued*)

Table 3 (Continued).

Citation	Level of Evidence	Risk of Bias	Study Devices	No. Patients	Study Design	Diagnoses	Age, mean (range)	Variables Provided
Fasth et al 2008[29]	6	High: Uncontrolled, open-label single arm; small sample; reliance on patient-/parent-reported QoL measures; recall bias; industry-sponsored	Crono Super-PID (Cane S.R. L., Italy)	12	Phase IV, prospective, open-label	PID	10.9 (1.7–17.1)	IgG levels; Health-related Quality of Life, local infusion-site reactions
Heimall et al 2016[30]	6	High: Open-label, single-arm crossover, no parallel control; small sample; preselected stable patients; reliance on AE reporting; industry-sponsored with author affiliations	Crono S-PID -50 (Cane S.R. L., Italy)	12	Phase IV, multicenter, open-label, single-sequence, crossover	PID	10.8 (7.1–14.5)	IgG levels; infection rate; local infusion-site reactions; demographics

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Study Type	Randomization	Blinding	Comparator	Sample Size	Outcome Type	Missing Data	Conflicts
Mechanical	🟡	🟡	🔴	🔴	🟡	🔴	🔴
Electronic	🔴	🔴	🔴	🔴	🔴	🔴	🔴

Figure 4 Risk of Bias Assessment Across Included Studies. Summary of Risk-of-Bias Assessment Across Included Mechanical and Electronic Infusion-System Studies. Colored circles represent the overall risk-of-bias assessment for each methodological domain across the included studies. Green indicates low risk of bias, yellow indicates some concerns, and red indicates high risk of bias. The assessments shown represent the predominant risk-of-bias judgment within each infusion-system category rather than individual study-level assessments.

Discussion

This systematic review compared mechanical and electronic infusion systems with respect to local infusion-site reactions and treatment performance. Across studies, mechanical infusion systems were consistently associated with lower reported proportions of swelling, redness, and soreness compared to electronic infusion devices.

The direction of findings was consistent across all evaluated outcomes, with mechanical infusion systems demonstrating lower reported proportions of swelling, redness, and soreness than electronic infusion systems. The consistency of these findings across multiple local tolerability outcomes suggests that the observed differences are unlikely to be attributable to a single isolated factor. However, differences in patient populations, immunoglobulin formulations, infusion protocols, publication era, and reporting practices may have contributed to the variability observed across studies and should be considered when interpreting the findings.

Table 4 Comparison of Swelling Between Mechanical and Electronic Infusion Systems

Infusion System Type	With Swelling	Without Swelling	Total
Mechanical	24 (23.1%)	80	104
Electronic	205 (61.4%)	129	334
Total	229	209	438

Table 5 Comparison of Redness Between Mechanical and Electronic Infusion Systems

Infusion System Type	With Redness	Without Redness	Total
Mechanical	34 (28.6%)	85	119
Electronic	147 (44.0%)	187	334
Total	181	272	453

Table 6 Comparison of Soreness Between Mechanical and Electronic Infusion Systems

Infusion System Type	With Soreness	Without Soreness	Total
Mechanical	24 (22.9%)	81	105
Electronic	173 (50.0%)	173	346
Total	197	254	451

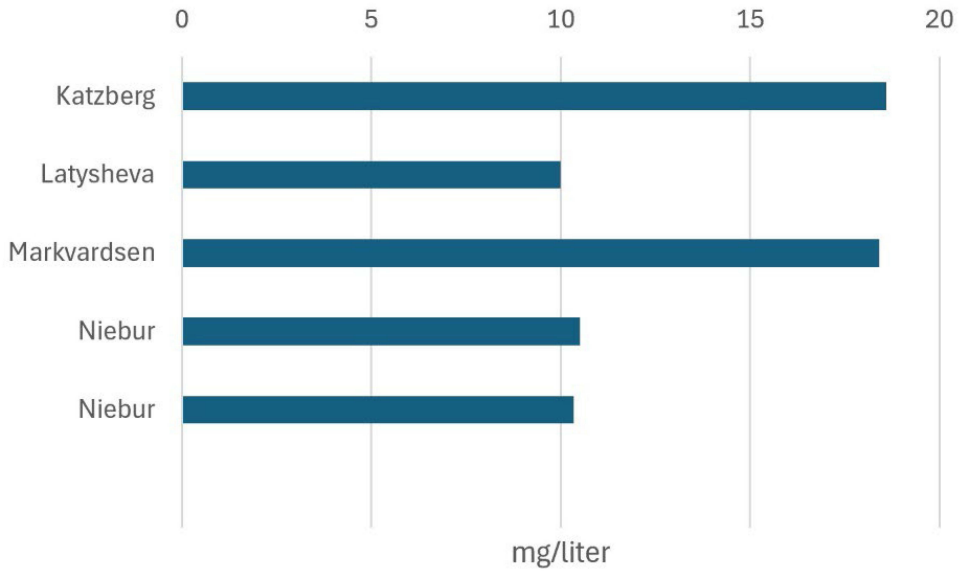

Figure 5 Mean IgG Levels by Study for Mechanical Infusion Systems.
Abbreviation: IgG, Immunoglobulin G.

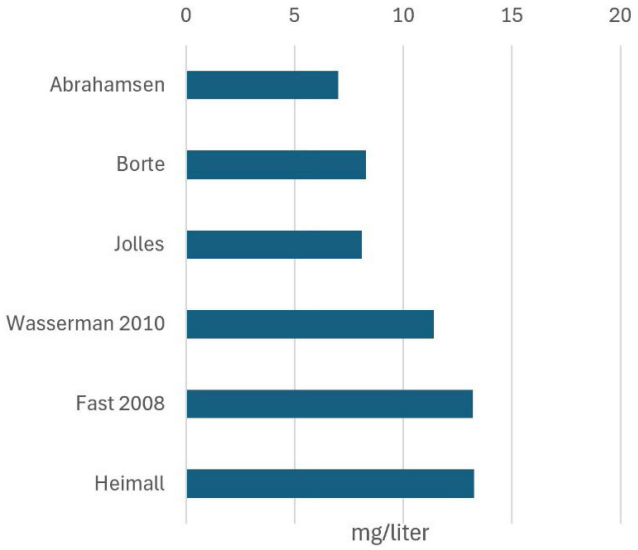

Figure 6 Mean IgG Levels by Study for Electronic Infusion Systems.
Abbreviation: IgG, Immunoglobulin G.

From a clinical perspective, the lower reported rates of infusion-site reactions with mechanical infusion systems may be particularly relevant in SCIg therapy, where long-term treatment adherence and patient comfort are important considerations. The skin-contacting components of SCIg administration systems are generally similar across delivery methods, as both mechanical and electronic systems typically utilize comparable subcutaneous needle or cannula sets, adhesive dressings, and administration tubing. Consequently, differences in local infusion-site reactions are unlikely to be explained solely by the materials in contact with the skin. Rather, they may be related to differences in how the medicinal product is delivered into the subcutaneous tissue, including infusion duration, flow characteristics, pressure profiles, and tissue exposure time.

One potential explanation for the lower rates of swelling, redness, and soreness observed with mechanical infusion systems relates to infusion dynamics. During SCIg administration, medicinal product (fluid) accumulates within the subcutaneous space, resulting in tissue expansion, transient edema, increased interstitial pressure, and reduced tissue compliance. These biomechanical changes may contribute to local discomfort and increasing tissue resistance during the infusion. Such effects are expected to occur regardless of infusion system and are primarily related to the interaction between the infused product and subcutaneous tissue rather than a pharmacologic effect of immunoglobulin itself. Mechanical infusion systems may offer advantages in this setting because their flow characteristics are inherently responsive to changes in tissue resistance, potentially reducing tissue stress as resistance increases. Although this hypothesis warrants further investigation, it provides a biologically plausible explanation for the consistently lower rates of local infusion-site reactions observed across studies.

With respect to treatment performance, both mechanical and electronic infusion systems achieved IgG levels consistent with therapeutic targets, supporting their effectiveness in delivering SCIg therapy. Importantly, the apparent reduction in local infusion-site reactions observed with mechanical infusion systems was not accompanied by evidence of reduced treatment performance. Although descriptively higher mean IgG levels were observed in studies utilizing mechanical infusion systems, these differences are difficult to interpret due to variations in baseline IgG levels, dosing strategies, and study populations, and should not be attributed solely to device performance. Collectively, these findings suggest that mechanical infusion systems may offer improved local tolerability while maintaining effective SCIg delivery, a combination that may be particularly valuable in long-term therapies where patient comfort and treatment adherence are important considerations.

In addition to structured literature reviews, real-world evidence studies and post-market safety surveillance programs may provide important complementary approaches for evaluating infusion-system-related safety and performance outcomes. Large observational cohorts and registry-based studies have been successfully used to characterize adverse event profiles associated with immunological therapies in routine clinical practice. Similar approaches could help further characterize infusion-system-related outcomes, including local infusion-site reactions, device usability, treatment adherence, and long-term patient experience across different SCIg delivery methods. Such evidence may complement controlled clinical studies by providing insight into device performance under real-world conditions. Future observational and registry-based studies may also help identify patient-, treatment-, and device-related factors associated with local tolerability and treatment success. Careful consideration of potential sources of bias and confounding inherent to non-randomized research will be important when evaluating comparative safety and performance outcomes.

Clinical Implications

- Mechanical infusion systems may be associated with lower reported rates of local infusion-site reactions (swelling, redness, soreness), although findings are variable across studies and should be interpreted as descriptive trends. Both mechanical and electronic infusion systems achieve IgG levels consistent with therapeutic targets, supporting their effectiveness in SCIg therapy.
- Infusion dynamics, including pressure and flow characteristics, may influence patient comfort and local tolerability and should be considered when selecting an infusion system.
- Reliable delivery of the prescribed dose remains essential for effective therapy; in the absence of direct delivery measures, IgG levels may serve as a practical indicator of performance in clinical studies. Device selection should be individualized, considering patient preference, age, patient tolerability, and specific infusion protocols.

Limitations

As a structured literature review, the study was designed to provide a comprehensive descriptive assessment of the available evidence rather than a formal systematic review with pooled-effect meta-analysis. Several limitations should be considered. First, no direct head-to-head studies comparing mechanical and electronic infusion systems were identified; therefore, conclusions are based on indirect comparisons across heterogeneous studies. Variability in study design, patient populations, immunoglobulin formulations, infusion protocols, and outcome definitions further limits comparability and introduces potential confounding.

Second, adverse event reporting was inconsistent across studies. Most studies focused on local infusion-site reactions, while other clinically relevant outcomes, such as needle set wear time, insertion-site complications, device malfunctions, ease of use, adherence, patient satisfaction, and health-economic outcomes, were infrequently reported or not reported in a standardized manner. In addition, performance was assessed primarily through achieved IgG levels because direct measures of dose delivery and infusion completion were not consistently available.

Third, the biological mechanisms underlying differences on local infusion-site reactions could not be evaluated. Variables that may influence local tolerability, including infusion duration, pressure characteristics, tissue resistance, and infusion dynamics, were not systematically reported. Consequently, any proposed explanations for differences between infusion systems remain hypothesis-generating and require confirmation in prospective comparative studies. In addition, the relatively small number of available studies, particularly those evaluating mechanical infusion systems, limits the robustness of comparisons.

Conclusion

SCIg administration is an established and increasingly preferred approach for the long-term management of PID, SID, and CIDP. Device selection represents an important factor influencing safety, tolerability, and overall patient experience.

This review found that mechanical infusion systems were consistently associated with lower rates of local infusion-site reactions compared with electronic systems. These findings should be interpreted as descriptive trends in the context of variability across studies. Because comparable subcutaneous needle or cannula systems are typically used across delivery methods, differences in local tolerability are unlikely to be explained solely by skin-contacting materials and may instead be related to infusion dynamics. Potential contributing factors include infusion duration, pressure generation, flow characteristics, and tissue exposure time; however, these mechanisms were not directly evaluated in the available literature.

Both mechanical and electronic infusion systems achieved IgG levels consistent with therapeutic targets, supporting their effectiveness in delivering SCIg therapy. Reliable delivery of the prescribed dose remains essential and should be considered alongside safety and usability when evaluating infusion systems.

In clinical practice, device selection should be individualized, taking into account patient-specific factors such as tolerability, ease of use, and lifestyle considerations. Further well-designed, head-to-head comparative studies are needed to better define differences in safety, performance, usability, and cost-effectiveness between mechanical and electronic infusion systems, as well as the role of infusion dynamics in influencing patient outcomes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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