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Impact of organizational interventions on reducing inappropriate intravenous immunoglobulin (IVIG) usage: A systematic review and meta-analysis

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ABSTRACT

Background: With increasing global use of intravenous immunoglobulin (IVIG), there is interest in its appropriate usage. Efforts to regulate IVIG usage have primarily taken the form of organizational interventions implemented in hospitals to monitor and improve physician prescribing. Similar interventions have proven effective in reducing the inappropriate and total hospital usage of other blood products, but their efficacy on IVIG use is less understood. Thus, we performed a systematic review of studies reporting the change in inappropriate IVIG use following such interventions in hospitals or regions.
Methods: A systematic search was carried out using MEDLINE and EMBASE (1966-June 2016) for English language studies if they 1) were primary research, 2) described an organizational intervention to target plasma, IVIG, or albumin, and 3) reported appropriateness of usage and total usage preand post-intervention. Review Manager v5.0 was utilized to perform a random-effects meta-analysis on eligible IVIG studies, where the risk ratio (RR) of inappropriate IVIG transfusion comparing pre- and postintervention periods was calculated with 95% confidence intervals (CI).
Results: Our search retrieved three retrospective cohort studies, where metaanalysis encompassing 2100 episodes of IVIG transfusion demonstrated no decrease in inappropriate IVIG use (RR 1.55, 95% CI 0.78–3.07). Heterogeneity between studies was considerable (I2 = 89%).
Conclusion: Organizational interventions were ineffective at changing inappropriate IVIG use, but more high-quality studies describing the effects of these interventions are required before any conclusions can be drawn. Futureresearch efforts should also be directed at evolving evidence-based IVIGguidelines to improve patient safety and burdens on healthcare systems

1. Introduction

Intravenous immunoglobulin (IVIG) is a blood product used as replacement therapy for patients with immune deficiencies and increasingly used as an immunomodulator. Both the number of IVIG prescriptions and the total amount of IVIG used continues to increase [1,2]. Furthermore, the variety of conditions for which IVIG is administered is expanding, resulting in varying levels of evidence of efficacy (Table 1). With few labeled indications for IVIG, much of its use is for off-label indications for which there is minimal evidence of efficacy. In nearly all descriptive studies examining prescribing practices in hospitals, off-label use is unexpectedly high and inappropriate use constitutes a significant portion of total IVIG infusions [1,3–6]. Inappropriate and ineffective treatments delay patient access to more effective treatments, and increase costs to healthcare systems [7,8]. Most importantly, IVIG infusions put patients at a 5–15% risk of experiencing adverse effects such as headache, fever/chills, myalgia, anxiety, tachycardia, hypotension, nausea, vomiting, and rash [9,10]. Rarer but more serious adverse events include hemolysis, infection, aseptic menin-

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Table 1
Categories of IVIG use.

Categories of Use	Examples
Labeled	Primary Immune Deficiency (PID)
	Secondary Immune Deficiency (SID)
	Idiopathic Thrombocytopenic Purpura (ITP)
	Chronic Inflammatory Demyelinating Polyneuropathy
Unlabeled –Potentially Indicated	Myasthenia Gravis
	Guillain-Barré Syndrome
	Multifocal Motor Neuropathy
	Multiple Sclerosis
	Stiff Person Syndrome
	Autoimmune Hemolytic Anemia
	Dermatomyositis
	Pemphigus Vulgaris
Unlabeled –Not Indicated	Unclassified Connective Tissue Disease
	Sepsis
	Kidney Transplant
	Acute Antibody-Mediated Rejection
	Hematopoetic Stem Cell Transplant in SID
	Bone Marrow Transplant

gitis, anaphylaxis, transfusion-related acute lung injury (TRALI), and thromboembolic events [9,10].

There is a need for practice guidelines coupled with interventions and prospective evaluation to reduce the inappropriate use of IVIG [11,12]. The impact of organizational interventions to reduce inappropriate use of blood products such as red blood cells (RBCs) and plasma has been previously studied [13–15]. The interventions vary and include: policy changes, approval processes and committees, request forms, education sessions, and audits. Although these alert and constrain physicians to the appropriate indications for transfusion, they only demonstrate short-term effectiveness [13]. There is debate over whether specific interventions are truly effective in changing physicians' transfusion practices, notably for reducing inappropriate IVIG use. Given the small number of labeled indications for IVIG and a smaller evidence base for efficacy in IVIG, interventions to reduce inappropriate use may be more successful for IVIG. To explore this, we performed a systematic review and meta-analysis to examine the efficacy of organizational interventions implemented to reduce inappropriate IVIG use.

2. Methods

2.1. Search strategy

We searched MEDLINE and EMBASE (Ovid Technologies Inc., New York City, NY) from 1966 to June 1 2016 for English-language studies of organizational interventions related to IVIG, albumin, or frozen plasma usage. The MEDLINE search was conducted by first exploding and combining the Medical Subject Heading (MeSH) terms related to our products of interest: *intravenous immunoglobulins*, *serum albumin*, *plasma*, and *blood transfusion*. This group of combined terms was then combined with two other groups: organizational interventions (keywords: *intervention*; *guidelines*; *process*; *forms*; *haemovigilance* and MeSH terms: *quality assurance*; *continuing education*; *drug utilization review*; *professional staff committees*; *program evaluation*; *computer-assisted decision making*; *clinical decision support systems*; *triage*) and intervention outcomes (MeSH: *physician's practice patterns*; *practice guidelines as topic*; *drug utilization*; *inappropriate prescribing*; *clinical competence*; *guideline adherence*; *off-label use*; *drug labeling*; *health services misuse*). A similar search was performed with EMBASE. The full search strategies can be found in the Supplementary Appendix. We reviewed reference lists of included studies to identify additional potentially relevant studies.

Our search strategy was initially constructed to identify and review interventions targeted at reducing plasma and plasma protein products (albumin and IVIG). This systematic review is restricted to studies of interventions for reducing IVIG use given that IVIG is used for both immunomodulatory and replacement therapies whereas albumin and plasma use is limited to replacement. Eligible studies examining organizational interventions to reduce albumin or plasma use will be analyzed separately.

2.2. Eligibility

We included studies if they 1) were primary research; 2) described an organizational intervention designed to target hospital use of at least one of three blood products (plasma, IVIG, albumin); and 3) reported appropriate, inappropriate, and total usage of products pre- and post-intervention. There were no restrictions on the basis of patient characteristics or study design.

Potentially relevant articles were imported into EndNote X7.2 (Thomson Reuters, New York City, NY) and screened independently for eligibility by two reviewers (C.D. and M.P.). All discrepancies were resolved by consensus and, if necessary, a third reviewer (C.M.H.) was consulted.

2.3. Data extraction and quality assessment

One reviewer (C.D.) designed and piloted a standardized data extraction form on ten randomly selected articles. Data extracted included: study characteristics, intervention characteristics, and number of appropriate, inappropriate, and total IVIG usages before and after the intervention. IVIG uses that were deemed "labeled" and "unlabeled but potentially indicated" were considered appropriate uses. Uses that were of "uncertain benefit" were also categorized as appropriate as it was use considered similar to being "potentially indicated". Uses that were "unlabeled and not indicated" or contained "insufficient information" were considered inappropriate uses.

Data from all included articles were extracted independently by two reviewers (C.D. and M.P.) into the web-based REDCap (Research Electronic Data Capture) software hosted at McMaster University [16]. All discrepancies in extracted data were resolved by consensus and, if necessary, a third reviewer was consulted (C.M.H.). To evaluate agreement between the two reviewers, a kappa test was performed using the web-based GraphPad Software (Graphpad Software Inc, La Jolla, CA).

2.4. Data analysis

Review Manager v5.0 (Cochrane, London, England) was used to perform a random-effects meta-analysis on eligible IVIG studies. A random-effects model was used given the predicted heterogeneity in studies. The risk ratio (RR) of inappropriate IVIG transfusion was calculated with 95% confidence intervals (CIs). Heterogeneity among studies was tested using a chi-square (X^2) test with a significance level of 0.05. The risk of bias of each eligible study was assessed using the Newcastle-Ottawa scale [17].

3. Results

The search retrieved 5581 unique titles and abstracts of which 136 were deemed to be potentially relevant. Manual searches of reference lists yielded an additional 4 articles for full text review. 92 studies were excluded upon full text review of the 140 eligible studies (Fig. 1). There was a high degree of agreement between reviewers in full text review (K = 0.90, 95% CI 0.82–0.98).

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