IgM-enriched Immunoglobulins in Sepsis

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III

Introduction

The role of intravenous immunoglobulins (IVIGs) as an adjunctive treatment in sepsis has been a subject of debate for years. The main critique has been the lack of randomized trials of adequate size showing the effect of IVIGs on outcome. For that reason, many of the guidelines on sepsis have not addressed the use of IVIG treatment. Likewise, the Surviving Sepsis Guidelines [1] did not consider the use of immunoglobulins in adult patients with sepsis.

As an adjunctive therapy in adults with sepsis, the use of immunoglobulins was first reported in the early 1980s [2], and studies completed through the 1990s were reviewed by the Cochrane collaboration [3]; this began the series of meta-analyses on immunoglobins in sepsis. In the Cochrane review of IVIGs for the treatment of sepsis, IVIGs were reported to significantly reduce mortality in patients with sepsis [3]. However the authors concluded that due to the small size of the trials, the evidence was insufficient to support a definitive conclusion. The Cochrane review also included a retrospective subgroup analysis comparing IgM-enriched IVIG with standard polyclonal IgG IVIG. In this subgroup analysis of 11 trials, a *post hoc* sub-analysis according to the type of IVIG demonstrated a greater reduction in mortality among patients given IgM-enriched immunoglobulin compared with standard immunoglobulin. To date, five newer meta-analyses on the use of polyclonal immunoglobulins as adjunctive therapy for sepsis have been published [4–8]. Compared with the Cochrane statement, these meta-analysis included more trials and study patients, including the large Score-Based Immunoglobulin G Therapy of patients with Sepsis (SBITS) study [9] using a standard IgG preparation in patients with severe sepsis. The results of each meta-analysis were very similar to the results of the Cochrane meta-analysis, which showed a reduction in mortality with a standard IgG IVIG administration, and a greater risk reduction with an IgM-enriched preparation.

In the latest meta-analysis, Kreymann et al. [4] summarized the data for two groups of studies using IgM-enriched IVIG or IgG IVIG. The authors included 8 smaller trials with IgM-enriched immunoglobulins, including 560 adult patients in whom the estimate of the pooled effect on mortality showed a relative risk of 0.66 (a 34 % relative reduction in mortality) with no substantial heterogeneity. The results were even better in neonate trials with 352 patients in 5 studies with a 50 % relative reduction in mortality. The comparison of IgM-enriched IVIG and IgG IVIG showed a strong trend in favor of IgM-enriched treatment both in adults and in neonates. As already reported in the Cochrane meta-analysis [3], these data again confirmed that preparations enriched with IgA and IgM (IgGAM) yielded better results than IgG

preparations. What is superior about IgM over IgG and why do IgM-enriched preparations seem to work better in patients with sepsis? To answer this question, the current review will address the mechanism by which IVIGs work in sepsis, and give brief information about the different nature of IVIGs and their effects on the treatment of sepsis. In addition to experimental evidence on the mechanism of action of immunoglobulins, we will mainly focus on the effects of IgM-enriched immunoglobulins and their clinical use in the management of sepsis.

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Mechanisms of Action of IVIG in Sepsis

IVIG is a therapeutic preparation of normal human polyclonal IgG obtained from a large number of healthy blood donors. The efficacy and tolerance of immunoglobulins from human plasma have been shown to be optimal since, compared with synthetic drugs, they have been shown to be highly specific. Initially introduced as a replacement therapy for patients with immune deficiencies, IVIG is now being used for the treatment of autoimmune and systemic inflammatory diseases. Besides these medical conditions, evidence suggests that many other conditions, such as inflammatory disorders with an imbalance in the cytokine network could benefit from IVIG treatment [10]. In sepsis, the use of IVIGs represents a therapeutic effort to positively modulate the immune response, thereby preventing organ dysfunction. Immunoglobulins might exert beneficial effects in sepsis by several mechanisms, like providing antibody against pathogen-specific lipopolysaccharides (LPS), enhancing phagocytic function, modulating cytokine responses, acting synergistically with antibiotics, and, most importantly, neutralizing endo- and exo-toxins [11].

Owing to their molecular structure, IVIGs react directly with viruses, bacteria, and toxins and also activate immunobiological activities in the body [10]. Studies have shown that IVIG preparations contain a broad spectrum of opsonic and neutralizing antibodies directed against a variety of antimicrobial agents. In addition to direct neutralization of these antigens, other modes of action contributing to the beneficial effect in systemic inflammatory diseases have been described for IVIG. These include blockade of Fc receptors on phagocytic cells, modulation of Fc receptor expression, interference with complement activation and the cytokine network, modulation of dendritic cell activity, and T and B cell activation. Thus, IVIGs have multiple modes of action which act synergistically [10].

Based on the differences in the amino acid sequences in the constant region of the heavy chains, immunoglobulins can be divided into five different classes (IgG, IgM, IgA, IgD, and IgE). Each class of immunoglobulin differs markedly in physical and biological properties from the other classes. IgM is the first class of antibody produced in the immune response. IgM is a larger molecule compared with IgG, and the concentration of IgM is 8–10 times lower than the concentration of IgG. Moreover, the half-life of the smaller IgG molecule is four times longer than that of the large IgM molecule [12].

Standard immunoglobulin preparations for intravenous administration contain class IgG immunoglobulin as the main component, while IgA and IgM immunoglobulins are present in small quantities. Although pure IgG preparations are known to be effective, IgM as well as IgG substitution appears desirable in cases like neonatal sepsis, which correlates with a physiologically-determined IgM deficiency in the newborn [13]. For IgM substitution, an intravenous IgM preparation (Pentaglobin, Biotest Pharma GmbH, Dreieich, Germany) was developed and introduced for clini-

cal use in 1985, comprised of IgG (76 %), IgA (12 %), and IgM (12 %) (IgGAM). The efficacy of this preparation has been demonstrated in various ways [13]. The immunoglobulin concentration and antibody activity of this product was tested, demonstrating 99 % immunoglobulin purity, with very low anti-complement activity, which accounts for its tolerability to the same degree as standard intravenous IgG preparations.

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Differences between IgG- and IgM-enriched Immunoglobulins

In vivo and *in vitro* studies have demonstrated that IgM is much more potent in general functions compared with IgG. The pentameric form of IgM has been suggested to contribute to superior efficacy in toxin neutralization and bacterial agglutination compared with IgG antibodies and has been shown to be very efficient at fixing complement and enhancing opsonization [14, 15].

A pre-eminent property of IgM is its capacity to produce pronounced activation of complement, which leads to irreversible damage of the bacterial membrane. More IgG molecules are required to damage the cell than IgM molecules. Moreover, the potency of IgM antibodies in the agglutination of large and complex structures, e.g., salmonella, is 10 times greater than that of IgG. In the same system, the killing of bacteria by IgM is more effective, since IgM activates 100 – 400 times more complement than IgG [12]. In the opsonization of bacteria, IgM has been shown to be 1000 times more active than IgG and IgM produces more antibody against endotoxin (LPS). The anti-LPS antibody content of commercial IVIGs was examined using LPS preparations from *Escherichia coli*, *Klebsiella*, and the *Pseudomonas aeruginosa* serotypes which occur most frequently in Gram-negative septicemia [16]. Three different IgG products and one IgM-enriched product were tested. The mean antibody levels were significantly higher in the IgM fraction of the IgM-enriched product compared with pure IgG products, which indicated that natural antibodies against bacterial LPS might belong primarily to the IgM class. The endotoxin neutralizing capacities of IgM and IgG were also assessed in an endotoxic shock model [17]. Maximal endotoxin inactivation was achieved after 15 min with the IgM-enriched preparation; however, the addition of two pure IgG preparations did not reveal a significant effect on endotoxin recovery. The inactivation was much lower with a standard IgG preparation than that obtained after the addition of the IgM-enriched immunoglobulin. Endotoxin-induced cytokine release from whole blood was not influenced by IgG; however, IgM administration significantly decreased the release of tumor necrosis factor (TNF)-α and interleukin (IL)-1 in a concentration-dependent manner. What about exotoxins? In an *in vitro* study [18], investigators compared the ability of different immunoglobulin preparations containing IgG, IgM, and IgA to neutralize the activity of streptococcal pyrogenic exotoxin (SpeA). All immunoglobulin preparations markedly inhibited the mitogenic and cytokine-inducing activity of SpeA. Moreover, the comparative neutralization effects of the IgM-enriched preparation on streptococcal exotoxin showed that both IgM and IgA are potent inhibitors of group A superantigens and pentaglobin containing IgGAM was significantly more potent on streptococcal exotoxin than the preparation containing only IgG.

The toxin inhibitory activity of intravenous IgGAM was studied in experimental endotoxemia induced by the intraperitoneal inoculation of a sublethal dose of *E. coli* and the subsequent intravenous administration of an antimicrobial agent [19]. The aim was to investigate whether a protective effect can be achieved in endotoxemia by

application of IgM-enriched polyclonal immunoglobulin. The prophylactic administration of IgGAM significantly attenuated the antibiotic-induced increase in endotoxin activity as compared to the albumin control group. This decrease in endotoxemia was also shown to be associated with reduced levels of circulating IL-6. This synergistic effect occurring following the combined administration of pentaglobin with antibiotics was also confirmed in an experimental model of fecal peritonitis [20]. The effect of pentaglobin and piperacillin individually and in combination was investigated with particular emphasis on the role of intervention timings on survival rates in septic rats. The combined treatment with piperacillin plus pentaglobin provided better results as compared to the individual effects. The best results occurred with the earliest (4 h) administration, but the drugs showed no protection if the treatment was delayed 8 h following induction of peritonitis, indicating the effectiveness of early treatment with intravenous IgGAM [20].

Another potential difference in the mechanism of action of IgG and IgM is their effects on endotoxin-induced capillary perfusion failure and the resulting tissue integrity and organ function. Evidence suggests that the endotoxin-induced interaction of leukocytes with the endothelium at the microcirculatory level is a major cause of the microvascular injury responsible for perfusion failure and organ dysfunction. In an experimental study [21], the *in vivo* effects of clinically-used immunoglobulin preparations on microcirculatory mechanisms were analyzed in an endotoxemia model. Both intravenous IgM and IgG preparations markedly attenuated the endotoxin-induced leukocyte adherence in arterioles and venules at 8 h of endotoxemia. At 24 h, however, intravenous IgM was capable of further reducing venular leukocyte adherence, whereas IgG did not show a protective effect compared with controls. The protective effect of IgM was also evident with the measurement of functional capillary density (FCD). IgM application significantly ameliorated the LPS-induced decrease in FCD, whereas intravenous IgG did not provide protection against microvascular perfusion failure. Very recently, the protective effects of IgM on tissue integrity following secondary hyperinflammatory tissue damage caused by LPS were evaluated in an established model of endotoxemia [22]. The augmentation of host defense by IgM was not associated with collateral tissue damage, thus IgM substitution had an especially beneficial effect on LPS-induced pulmonary damage. The pulmonary protective effects of IgM substitution were demonstrated histologically and on a score-based evaluation. Significantly reduced alveolar damage, especially with respect to alveolar edema, interstitial edema, and hemorrhage was evident with the administration of IgM-enriched immunoglobulin. Similar pulmonary protective effects were shown in a rat acute respiratory distress model. Lachmann et al. [23] showed that translocation of *Klebsiella pneumonia* from the lung into the systemic circulation was reduced after IgM application, signifying a protective IgM effect on the alveolar-capillary barrier.

Clinical Significance of IgM-enriched IVIG

Clinical studies with IgM-enriched immunoglobulins in a mixed patient population of septic patients or more homogeneous groups for prophylactic use (primarily after cardiac surgery) showed a trend toward reduced morbidity and mortality; however, the lack of a significant difference in these studies was attributed, at least in part, to the small number of patients included in the studies (**Table 1**). After its introduction as an endotoxin-neutralizing technology, intravenous IgM-enriched immunoglobu-

Table 1. Randomized control trials of IgM-enriched IVIG therapy in patients with sepsis

Reference	Population	No. of Patients	Mortality	p value
Schedel et al. [24]	Gram-negative sepsis patients with high endotoxin levels	69	IVIG: 1/27 Control: 9/28	0.012
Tugrul et al. [25]	Medical and surgical severe sepsis patients	42	IVIG: 5/21 Control: 7/21	0.73
Karatzas et al. [26]	Medical and surgical severe sepsis and septic shock patients	68	IVIG: 8/34 Control: 14/34	0.05
Rodriguez et al. [27]	Intra-abdominal sepsis patients	56	IVIG: 8/29 Control: 13/27	0.17
Hentrich et al. [28]	Neutropenic patients with hematologic disorders with sepsis	211	IVIG: 27/103 Control: 29/103	0.93

lin was assessed in a homogeneous septic patient population with high endotoxin levels [24]. Patients within 24 hours after the onset of septic shock with endotoxemia were randomized to receive IgM-enriched immunoglobulins with the hypothesis that eliminating endotoxin as early as possible might improve the clinical course of septic shock. The study was discontinued after the evaluation of the data from 55 patients, since the difference between the mortality rates (4 % vs. 32 %) was statistically significant in favor of the therapy. There was a statistically significant decrease in the APACHE II score beyond the 5th day after inclusion and the serum concentration of endotoxin was significantly reduced in IgM-treated patients within 24 hours after inclusion. In a mixed patient population with severe sepsis, our group evaluated the effects of IgM-enriched IVIG treatment on progression of organ failure and development of septic shock [25]. The patient population had severe sepsis and was obtained from the medical and surgical ICUs, regardless of the causative organism. Patients randomized to receive pentaglobin were treated for 3 consecutive days and followed up for 8 days in terms of inflammatory parameters and organ dysfunction. Mortality was not an endpoint in the study. A marked trend in favor of IgGAM treatment was demonstrated; however, the power of the study was not sufficient to make any clear conclusion. Procalcitonin (PCT) levels, as a marker of the severity of the inflammatory response, declined consistently in the treatment group, however this decline did not correspond with the clinical course, which was reflected by unchanged sequential organ failure assessment (SOFA) scores throughout the study, yet a trend in reduced incidence of septic shock and 28-day mortality was evident. In a similar protocol including 68 ICU patients with severe sepsis, Karatzas et al. [26] reported a significant reduction in mortality, especially in the IgM-enriched immunoglobulin-treated patients with an APACHE II score ranging between 20 and 29.

Most recently, the impact of high dose IgM-enriched immunoglobulin and antibiotic therapy was assessed in a more homogeneous group of critically ill patients with proven intra-abdominal sepsis [27]. The administration of intravenous IgM-enriched immunoglobulin in addition to antibiotic therapy produced a 20 % reduction in mortality, although this difference was not statistically significant. In the subset of patients with appropriate antibiotic therapy, a significant reduction in the mortality of IVIG treated patients was reported with reductions in the relative and absolute risk of death by 74 and 25 %, respectively.

One of the largest studies on the use of IVIG in septic patients with chemotherapy-induced severe neutropenia has been recently published [28]. Two hundred eleven neutropenic patients with hematologic malignancies were randomized to receive intravenous IgGAM or albumin for 3 consecutive days. The study failed to document any benefit of IVIG therapy based on the 28-day mortality rate. Likewise, there was no significant difference in the duration of organ failure between the two arms; however, in all patients who survived with failing organs, there was a trend favoring intravenous IgGAM treatment. The choice of study population included in this trial [28] has been questioned with respect to representing the precise population of septic patients for IVIG treatment. These were low grade sepsis patients showing none or one organ failure with a relatively low mortality, and it has been suggested that these patients may not represent the target population for IVIG treatment to show any benefit on mortality.

Recently, the results of two large studies on the effects of standard G class IVIG treatment on a target group of sepsis patients (SBITS) [9] and post-cardiac surgery patients with severe systemic inflammatory response syndrome (SIRS) have been published [29]. The SBITS study revealed no reduction in mortality by administration of intravenous IgG in the entire study population, or in the subgroups. Given the statistical power, the study did not bolster the hope for IVIG therapy in septic patients. These results were further supported by a second large study in post-cardiac surgery patients with severe sepsis (the Early Supplemental Severe SIRS treatment with IVIG in score-identified high-risk patients after Cardiac Surgery study, ESSICS) [29]. The investigators of the SBITS and ESSICS studies have claimed that this failure with intravenous IgG does not necessarily exclude a survival benefit of IgM-enriched IVIG preparations, as suggested in previous meta-analyses [4–8].

The prophylactic use of IVIGs has been considered in surgical patients to reduce the incidence of infection and occurrence of sepsis and septic shock; however, results have been conflicting. In a clinical trial, Pilz et al. [30] showed that early supplemental IVIG treatment improved disease severity and may improve prognosis in prospectively APACHE II score-identified high-risk post-cardiac surgical patients. The same group [31] carried out a randomized prospective trial to compare the clinical course using a polyvalent IgG versus an IgGAM preparation in these high risk post-cardiac surgery patients. The study endpoints gave similar results for both immunoglobulin treatment regimens; however, with respect to serum IgM, only the IgGAM preparation led to significantly increased levels. Polyclonal IgM-enriched immunoglobulins did not significantly reduce the mortality rate in the overall study population; however, in the subgroup of patients with severe sepsis, they significantly improved the survival rate [32].

The prophylactic use of IgM-enriched solutions has been considered in high risk cardiosurgical patients to reduce the rate of infectious complications after open heart surgery. It has been suggested that the occurrence of postoperative infections is related to a pre-existing impairment of the immune system. Pre-operative anergic patients showing impaired cutaneous delayed type hypersensitivity responses were chosen as a high risk group for postoperative infection, and randomized to receive IgGAM 4 hours after surgery [33]. The infection rate was higher in the anergic patients compared to the normergic patients, and there was a significant reduction in infectious complications with IgM-enriched immunoglobulins in the anergic group compared with the control group [33]. Further studies compared two different IVIG preparations (IgG versus IgGAM), rather than two groups of patients treated with or without IVIGs [31, 34]. Two studies compared the efficacy of stan-

dard IgG and IgGAM in sepsis or in post-cardiac surgical patients at high risk for sepsis. No significant differences were noted between the two preparations in these patients. In the sepsis trial [34], patients treated with either IgG or IgGAM were compared with untreated controls, and there was a significant reduction in mortality with IgGAM when compared with controls, whereas no significant benefit was demonstrated for the standard IgG group.

An additional interesting finding is the beneficial effects of early treatment with IgM-enriched immunoglobulins on critical illness polyneuropathy (CIP) in patients with Gram-negative severe sepsis and septic shock, which has not yet been described for adjunctive intravenous IgG. In a retrospective study evaluating the incidence of CIP in patients with Gram-negative sepsis and organ dysfunction [35], investigators reported that patients who had been treated with IgGAM showed no signs of CIP during electrophysiologic examination. Similar results were also demonstrated in the SBITS trial [9], in which a shorter duration of mechanical ventilation was correlated with IVIG treatment. Amelioration in the motor response accounted for the effect on critical illness neuropathy, which might explain the shorter duration of mechanical ventilation in the treatment arm.

Conclusion

After more than 25 years of work examining IVIG therapy in sepsis, there are no recommendations for IVIG in the latest guidelines. A tangible explanation is that those studies with positive results were all small trials of low quality and the largest trial (SBITS) did not show the expected benefit with the standard IgG preparation. However, does this also apply to IgM-enriched immunoglobulins? There is enough *in vivo* and *in vitro* evidence showing the superiority of IgM-enriched IVIGs in experimental sepsis, and the clinical data are certainly not negligible and deserve to be considered. There may be some questions and concerns in terms of the power and the quality of the studies; however, no trial with IgM-enriched immunoglobulins demonstrated significantly different results, and tests of heterogeneity were not significant among the trials. Moreover, the latest meta-analyses, including 8 trials with nearly 600 patients, raised the possibility of a significant benefit with the use of IgM-enriched immunoglobulins in adult and neonatal septic patients [4].

It is clear that to better elucidate which patients would benefit from IgM-enriched immunoglobulin treatment, further trials are necessary. For the time being, the data suggest that the patients most likely to benefit from IgM-enriched IVIG are surgical ICU patients with Gram-negative septic shock. We believe that there is a need for larger clinical trials to confirm the effectiveness of this product in reducing mortality in sepsis. However, there is a question to be answered concerning the design of these trials: Will single-center, well-designed randomized controlled trials be adequate to obtain conclusive data concerning IgM-enriched IVIG therapy, or is it unavoidable that a large multicenter randomized controlled trial be called for in the next sepsis guidelines?

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