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Original Article

Opsonophagocytic Antibodies of Intravenous Immunoglobulin Preparations against Seven *Streptococcus agalactiae* Serotypes

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ABSTRACT

Purpose: Group B streptococcus (GBS) is a causative organism of invasive infections in neonates and pregnant women as well as in non-pregnant adults. Among 10 known serotypes of GBS, uncommon serotypes, such as IV and VI to IX, can cause invasive infections in immunocompromised patients. However, opsonophagocytic antibodies against these serotypes in human sera and intravenous immunoglobulin (IVIG) have not yet been studied. IVIG therapy is used to treat or prevent invasive infections in patients with primary antibody deficiencies. Here, we analyzed the activity of opsonophagocytic antibodies against GBS in IVIG preparations.
Methods: Opsonophagocytic antibody activity (opsonic index [OI]) against seven GBS serotypes (II and IV to IX) was evaluated in 16 commercially available IVIG preparations using the opsonophagocytic assay (OPA) in HL-60 cells and baby rabbit complement assay during 2015–2016 in South Korea (UAB GBS OPA, at http://www.vaccine.uab.edu).
Results: The estimated serum trough levels of OIs against GBS exceeded the limit of detection (≥4) in all IVIG preparations. For serotype VII, the serum levels of OIs were 6–136, the lowest among all serotypes. An IVIG dose of 400 mg/kg was found to be appropriate for immunocompromised individuals to prevent invasive GBS infections.
Conclusions: Most immunoglobulin products displayed high levels of opsonophagocytic activity against GBS, except for serotype VII. IVIG preparations could serve as a therapeutic or immunomodulatory agent for immunocompromised individuals.

Keywords: *Streptococcus agalactiae*; Opsonin; Phagocytosis; Immunoglobulins; Immunocompromised host

INTRODUCTION

Streptococcus agalactiae (group B streptococcus [GBS]) is the causative agent of several invasive diseases such as meningitis and pneumonia in infants, pregnant women, immunocompromised adults, and the elderly.[1] Capsular polysaccharides (CPS) are well-studied, important virulence factors that contribute to GBS pathogenesis.[2] Immune response against GBS involves

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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opsonophagocytosis mediated by serotype-specific antibodies against CPS. At present, 10 serotypes (Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX) are recognized based on CPS typing.[3,4] Of these, serotype V has emerged as an important disease-associated serotype, whereas serotypes IV, VI, VII, and VIII have rarely been isolated from patients in the United States.[5,6]

Uncommon serotypes such as IV and VI to IX are associated with invasive diseases in immunocompromised individuals. For example, serotype IV has been recently implicated in adult and neonatal invasive diseases.[7] Furthermore, type IX strains can cause neonatal infections[8,9] and serotypes VI and VIII are prevalent in pregnant women in Japan.[10]

From 1996–2005, GBS was the most common pathogen of invasive bacterial infections (48.1%) and bacterial meningitis (47.6%) in immunocompetent infants younger than 3 months of age in a hospital-based multicenter study in Korea.[11] In this multicenter study of Korea, the proportions of late-onset GBS neonatal infection cases (54.2%) were higher than that of early-onset neonatal infection cases (33.3%).[12] GBS continued to be the most common cause of invasive bacterial infection up to 2013.[13] In most GBS infection cases of neonates, antibiotics were used as treatment. However, the delayed immunoglobulin synthesis and low rate of transplacental antibody transfer in neonates suggest that intravenous immunoglobulin (IVIG) may be a useful adjunctive therapy for treating GBS infections. In addition, IVIG may reduce the morbidity and mortality that is associated with GBS infections in high-risk neonates.[14]

IVIG replacement therapy has been used to prevent invasive infections in patients with primary antibody deficiencies (PAD).[15-17] However, no study has evaluated the specific functional antibodies against GBS that cause invasive infection in neonates, infants, the elderly, and patients with PAD. In addition, opsonophagocytic antibodies against GBS serotypes in human sera and IVIG preparations have rarely been studied.

We have previously reported functional antibodies in IVIG preparations against GBS serotypes Ia, Ib, and III.[18] In the present study, the opsonic indices (OIs) of functional antibodies to GBS serotypes II, IV, V, VI, VII, VIII, and IX was estimated in 16 commercial IVIG preparations from Korea and their ability to protect patients with PAD receiving the IVIG therapy was determined.

MATERIALS AND METHODS

1. IVIG preparations

Sixteen commercially available IVIG preparations obtained from two Korean manufacturers during 2015–2016 were analyzed (10 preparations from Korea A and 6 preparations from Korea B). These were treated with cold ethanol or detergent to purify the IVIGs. All IVIG products were formulated as liquids at a concentration of 50 mg/mL IgG.[19]

2. GBS bacterial strains

Seven serotypes II, IV, V, VI, VII, VIII, and IX of GBS were used in the analysis (**Table 1**). All strains were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). GBS strains were re-identified based on the presence of gram-positive cocci in pairs or short chains, beta hemolysis on blood agar plates, catalase-negative results, and Christie-Atkins-Munch-Petersen (CAMP) test, which is based on the formation of CAMP factor that

Table 1. GBS target strains for opsonophagocytic assay

GBS serotype	Strain name	Source
II	NCTC818	ATCC
IV	GBS NCTC1/32	ATCC
V	2603 V/R	ATCC
VI	BAA-2671	ATCC
VII	BAA-2670	ATCC
VIII	GBS 16-29	ATCC
IX	BAA-2668	ATCC

Abbreviations: GBS, group B streptococcus; ATCC, American Type Culture Collection.

increases the β-hemolysis zone produced by *Staphylococcus aureus*. The GBS serotypes of target strains were reconfirmed using a slide latex agglutination test (Denka Seiken, Tokyo, Japan) at the Ewha Center for Vaccine Evaluation and Study. All target strains were stored at −80°C in 0.5 mL of Todd–Hewitt broth with 15% glycerol.

3. Opsonophagocytic assay (OPA) for antibodies against GBS

Duplicate samples of IVIG (20 μL) were serially diluted (1:3) in opsonization assay buffer B (OBB; Hanks' balanced salt solution [with magnesium and calcium] containing 0.1% gelatin and 5% defined fetal bovine serum [Thermo Fisher Scientific, Waltham, MA, USA]) in 96-well round-bottom plates. Frozen working stocks of each target strain were thawed and washed twice with OBB, followed by centrifugation at 12,000 *g* for 2 minutes in a microcentrifuge. A diluted bacterial solution was prepared by adding an appropriate volume of the bacterial stock solution to 10 mL of OBB to obtain an approximate concentration of 1×10^5 colony-forming units (CFUs)/mL. Next, 10 μL of the bacterial solution was added to each well, and the plates were incubated at room temperature for 30 minutes on a mini-orbital shaker (700 rpm). After incubation, 10 μL of baby rabbit complement (BRC; Pel-Freez Biologicals, Rogers, AR, USA) was added to the wells, except for control A wells, to which 10 μL of heat-inactivated BRC (heated at 56°C for 30 minutes) was added. Forty microliters of differentiated HL60 cells (containing 4×10^5 cells) were added to all wells, and the plates were incubated for 45 minutes in a 5% CO_2 incubator at 37°C on a mini-orbital shaker (700 rpm) in a single layer. We ensured not to open the incubator frequently to maintain a constant CO_2 percentage. After the incubation period, the plates were placed on ice for 20 minutes to stop the phagocytic process. Afterward, 5-μL aliquots of the reaction mixture from each well were spotted onto THYA-NR plates (Todd–Hewitt agar [1.5%] with yeast extract containing neutral red [30 μg/mL] and 1 M Tris solution [0.02 M]), and the plates were incubated (37°C/5% CO_2) overnight in an inverted position for 16 to 18 hours. After incubation, the plates were removed from the incubator and kept at room temperature for 4 to 5 hours, which decreased the background color. The number of surviving colonies on the plates was counted using the NICE colony counting software (National Institute of Standards and Technology's Integrated Colony Enumerator; National Institute of Standards and Technology, Gaithersburg, MD, USA). The OIs were calculated using linear interpolation. An Excel-based data processing program was used to transfer the colony counts to an "opsonization index" program ("opsotiter3" from the UAB reference laboratory). The OI value was defined as the reciprocal of the interpolated dilution of serum that killed 50% of the bacteria. If an undiluted serum sample killed 50% of the bacteria, the OI value was 4 in our system.

4. Estimated trough titers of specific antibody in the recipients' sera

Estimated trough titers of specific antibodies in the recipients' sera were calculated with the following formula, assuming that 400 mg/kg IVIG was infused into each patient with PAD[19]:

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Estimated Trough Titer of Specific Antibody=0.5×0.4×0.2×Antibody Titer

The factor 0.4 assumes 40% immunoglobulin in the intravascular compartment and that this number is at equilibrium. We briefly explain the components of this equation, which is based on a 22-day half-life of IVIG preparation and the assumption that the last infusion occurred 26 to 27 days before sampling.

Estimated Trough Value of Specific Antibody=0.5×Level at Equilibrium

Level at Equilibrium=0.4×Peak Value after Intravenous Infusion

$$\text{Peak Value} = \frac{\text{N}}{(40\ \text{mL plasma/kg}) \times \text{Patient Mass (kg)}}$$

$$= \frac{(8\ \text{mL/kg}) \times \text{Antibody Titer}}{(40\ \text{mL plasma/kg}) \times \text{Patient Mass (kg)}}$$

$$= 0.2 \times \text{Antibody Titer}$$

where N indicates the total dose infused into the patient (400 mg/kg IVIG preparation), and the concentration of IVIG preparations examined in this study was 50 mg/mL.

5. Statistical analysis

For each serotype, the geometric mean indices (GMIs) and 95% confidence intervals (CIs) were calculated. The differences in the GMIs among the IVIG preparations were analyzed using the Kruskal-Wallis test and the Mann-Whitney U test. Seropositivity was defined as the presence of detectable OIs (≥4). Differences were considered statistically significant at a *P*-value of <0.05. Statistical analyses were performed using SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA).

RESULTS

The OIs of each IVIG preparation against seven GBS serotypes (II, IV, V, VI, VII, VIII, and IX) were evaluated using GBS OPA at the Ewha Center for Vaccine Evaluation and Study. The GMIs and associated 95% CIs were calculated for each serotype.

1. OIs to serotype II, IV, V, VI, VII, VIII, and IX GBS

The OIs against seven GBS serotypes in 16 IVIG preparations are shown in **Table 2** and **Fig. 1**. The OI values were 592–956 (serotype II), 1,091–2,141 (serotype IV), 1,938–7,262 (serotype V), 292–628 (serotype VI), 6–136 (serotype VII), 331–628 (serotype VIII), and 686–2,398 (serotype IX). None of the IVIG preparations exhibited undetectable OI values (<4). The GMI values were not significantly different between the Korean A and B manufacturers for all seven serotypes (**Table 2**). The estimated serum trough levels of OIs against GBS exceeded the limit of detection in all IVIG preparations. For serotype VII, the serum levels of OIs were 6–136, the lowest among all serotypes.

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Table 2. OIs and geometric mean indices of IVIG preparations against GBS serotypes

IVIG	GBS serotype						
	II	IV	V	VI	VII	VIII	IX
OI of IVIG							
Korea A 01	621	1,379	3,315	440	10	418	688
Korea A 02	592	1,302	2,772	539	38	504	946
Korea A 03	734	1,563	2,769	323	13	394	753
Korea A 04	756	1,579	2,598	492	33	443	1,165
Korea A 05	878	1,793	3,520	292	48	460	962
Korea A 06	956	1,829	3,517	572	43	628	1,207
Korea A 07	935	1,536	2,965	454	42	489	1,421
Korea A 08	647	1,975	4,176	296	63	531	2,398
Korea A 09	687	1,091	2,473	308	52	526	1,670
Korea A 10	616	1,179	1,938	476	6	331	686
Korea B 01	661	1,511	3,334	529	47	433	1,248
Korea B 02	600	1,735	4,992	628	19	479	1,314
Korea B 03	804	1,539	3,922	578	63	475	730
Korea B 04	815	2,141	7,262	433	11	453	1,400
Korea B 05	739	1,719	3,196	453	136	600	809
Korea B 06	935	1,469	2,117	352	21	471	1,139
Geometric mean indices (95% CI)*							
Korea A	731 (654–816)	1,498 (1,327–1,688)	2,942 (2,569–3,367)	407 (345–478)	28 (16–46)	466 (416–520)	1,100 (854–1,415)
Korea B	751 (661–853)	1,672 (1,495–1,869)	3,840 (2,743–5,376)	486 (411–577)	34 (17–73)	482 (441–528)	1,075 (866–1,335)
Seropositive rate, No. (%)							
Korea A (10)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)
Korea B (6)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)

Abbreviations: OI, opsonization indice; IVIG, intravenous immunoglobulin; GBS, group B streptococcus; CI, confidence interval.
*No differences according to manufacturer within each serotype ($P>0.05$).

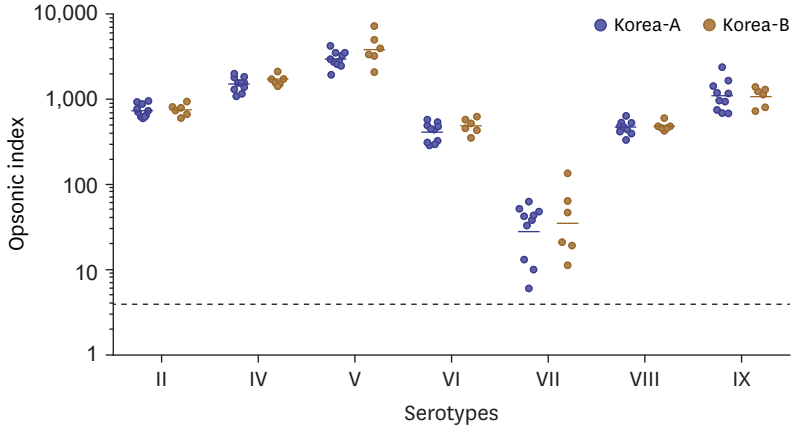

Fig. 1. Opsonic indices against seven group B streptococcus serotypes in various intravenous immunoglobulin preparations from 2 different manufacturers in Korea (Korea-A and Korea-B). Dashed line represents the lower limit of detection of opsonic index, 4. Horizontal bar represents geometric mean indices of specific antibody levels to each serotype.

DISCUSSION

GBS causes invasive infections in neonates, pregnant adults, and non-pregnant adults with underlying or chronic diseases.[8] Intrapartum GBS screening and antibiotic prophylaxis have reduced the incidence of early onset (0–6 days) of neonatal GBS diseases such as meningitis and sepsis.[20] However, GBS neonatal infections are still considered a major public health concern owing to high morbidity and mortality. The incidence of late-onset (7–90 days) infection has remained considerably stable, ranging from 0.25 to 0.5 per 1,000 live births.[21]

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In addition, the incidence of GBS infection in non-pregnant adults, particularly the elderly and immunocompromised patients, has increased from 8.1 cases/100,000 persons in 2008 to 10.9 cases/100,000 persons in 2016 in the United States. Among the cases with invasive GBS infection, 94.6% were hospitalized, 27.3% needed intensive care, and 5.6% were fatal in 2016. The incidence was higher in men than in non-pregnant women. This factor may be related to higher rates of important underlying conditions among men, such as diabetes or smoking. Incidence remains highest in persons aged 80 years or older, who accounted for 17.7% of total cases. The percentage of patients with invasive GBS infection who had underlying condition (i.e., obesity, diabetes) increased from 90.7% in 2008 to 94.6% in 2016.[22]

Preliminary epidemiological studies have reported an association between low concentrations of maternally derived antibodies against GBS CPS and enhanced susceptibility of neonates to GBS infection.[23] Similar to the protection against other encapsulated bacteria, protection against GBS involves antibody-mediated opsonization by phagocytes and complement-mediated bacteriolysis. We used the UAB GBS OPA to develop a protocol using human sera with 10 serotypes of bacteria at the Ewha Center for Vaccine Evaluation and Study in 2017.

Recent studies have evaluated the activity of functional antibodies against *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* in IVIG.[24-26] In addition, our group studied opsonic antibodies against GBS Ia, Ib, and III serotypes in IVIG.[18] However, no study has been conducted on functional antibodies against other GBS serotypes that cause invasive infections in neonates, infants, the elderly, and patients with PAD. We found that several commercial IVIG preparations had functional antibodies to serotypes II, IV, V, VI, VII, VIII, and IX GBS. Most immunoglobulin preparations displayed high opsonophagocytic activity against GBS, except for serotype VII.

Human IVIG was first licensed for the treatment of PAD in 1981.[27] IVIG is usually recommended at a dose of 400 to 600 mg/kg every 3 or 4 weeks, targeting an IgG trough of 500 to 750 mg/dL.[28] Although IVIG therapy improves the survival and functional status of patients with PAD, substantial variations in specific antibody titers to different pathogens have been reported.[29,30]

IVIG is a serum product formed by pooling the immunoglobulins obtained from approximately 1,000 to 100,000 healthy donors. It comprises antibodies against a wide spectrum of pathogens and self-antigens and therefore reflects the collective exposure of the donor populations to their environment.[31] The presence of functional antibodies to GBS II, IV, V, VI, VII, VIII, and IX serotypes in commercial IVIG preparations was expected because GBS is a human commensal in the gastrointestinal and genital tracts, which does not commonly cause infection or disease. However, large variations exist in the colonization rates of GBS among different populations and countries.[8] For instance, 6.3%–11.5% of pregnant women in South Korea are reported to be carrying GBS.[32-34] In the U.S, the large cohort of all births over a 12-year period (2003–2015) demonstrates a GBS colonization rate of 21.6%.[35] In China, where 49,908 pregnant women were enrolled between 2014 and 2017, the GBS colonization rate was 13.9%.[36] Therefore, the titers of pathogen-specific antibodies in IVIG may differ according to the donor population owing to the cumulative environmental exposure to infectious agents.

Because IVIG comprises a repertoire of antibodies against a wide range of antigens, IVIG replacement therapy is an effective prophylactic treatment for patients with PAD.[37] However,

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it is necessary to identify the specific antimicrobial activity and protective titers of functional antibodies against particular microbial pathogens in commercial IVIG preparations before using them in patients with sepsis and other invasive infections. Therefore, we studied the functional protective antibodies against seven GBS serotypes in Korean IVIG preparations to treat invasive diseases in patients with PAD.

The present study had certain limitations. First, although no protective threshold has been established against GBS, an OPA titer of 8 serves as a reliable threshold against the majority of pneumococcal serotypes.[38] Moreover, GBS serotype-specific antibody titers reported in recent studies[39,40] could be useful for developing appropriate cut-off values. In addition, we do not know what level of functional antibody means protective level of antibody. Second, we included IVIG preparations only from Korea. Continuous monitoring of antibody titers included in more IVIG preparations from multiple countries will be helpful to establish therapeutic and preventive measures to invasive GBS diseases in the future. Furthermore, studies to assess the presence and activity of functional antibodies in the sera of PAD patients are warranted. Evaluation of the prevalence of GBS serotype-specific OIs in pregnant women before delivery may predict the risk of GBS infection in newborn infants.

In conclusion, we performed OPAs to evaluate the OIs of GBS II-, IV-, V-, VI-, VII-, VIII-, and IX-specific antibodies in commercial Korean IVIG preparations. Based on the results, we conclude that the tested commercial IVIG preparations had sufficient functional antibodies against seven GBS serotypes that could protect patients with PAD receiving IVIG replacement therapy.

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요약

목적: *Streptococcus agalactiae* (group B streptococcus [GBS])은 신생아, 임산부 및 성인에서 침습성 감염의 주요 원인균이다. 면역체계가 손상되거나 약화된 경우, 잘 알려진 10개의 GBS 혈청형 중 흔하지 않은 IV, VI-IX에 의해 침습적인 질환이 발생할 수 있다. 그러나, 지금까지 사람의 혈청 및 정주용 면역글로불린(intravenous immunoglobulin, IVIG) 제제 중 GBS의 흔하지 않은 혈청형에 대한 옵소닌 항체(opsonophagocytic antibody) 활동은 연구되지 않았다. 면역글로불린 치료 요법은 일차 항체 결핍증(primary antibody deficiency, PAD) 환자의 침습적 감염을 치료하거나 예방하는 데 사용된다. 이 연구에서는 면역글로불린에서 GBS에 대한 옵소닌 항체 활성을 평가하고자 한다.

방법: 2015–2016년 국내 두 회사에서 사용가능한 16개 면역글로불린에 대하여 7개 GBS 혈청형 (II 및 IV-IX)에 대한 옵소닌 항체 활성도(opsonic index [OI])를 HL-60 세포와 아기토끼 보체를 사용하여 옵소닌 분석법(opsonophagocytic assay)을 통해 분석하였다. (UAB GBS OPA, http://www.vaccine.uab.edu).

결과: 모든 면역글로불린 제제에서 GBS에 대한 OI의 검출 한계점(≥4)을 초과하였다. 혈청형 VII의 경우, OI 값은 6–136으로 모든 혈청형 중에서 가장 낮았다. IVIG의 최저 수준(trough level)을 추정해볼 때, 일반적인 면역글로불린 용량 (400 mg/kg)은 PAD 환자에게 침습성 GBS 감염을 예방하기 위한 적합한 용량으로 보인다.

결론: 국내에서 사용중인 면역글로불린 제품은 GBS에 대한 높은 수준의 옵소닌 항체 활성을 나타냈다. 면역글로불린은 PAD 환자에게 유용한 치료 또는 예방조치가 될 수 있을 것으로 보인다.

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