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Research Article

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Immunoglobulin Therapy in Infertile Women: Safety and Tolerance

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Abstract

Introduction and Objectives: *According to most recent surveys, infertility rates are very high in Spain. Even so, current therapeutic options for increasing fertility are challenging. Immunological causes of infertility such as an increase in natural killer cells have been studied in recent work, for example by using immunoglobulins. Providing care and support for women during such treatments is the traditional responsibility of nursing professionals. The objective of this study was to understand how patients adapt to treatments with immuno globulins at FIV Valencia[i].*

Methods: *Retrospective observational study which monitored 40 intravenous immunoglobulin infusions: 400 mg/kg in 27 cases and 200 mg/kg in 13 cases. The state of women's health was studied with home monitoring, and women's answers about their health statuses were measured using Liker scales with four values. These identified the occurrence of symptoms and the need for analgesic therapy. The data was analyzed using SPSS.*

Results: *Vital sign monitoring reflected values within the normal limits during all 40 infusions; the figures decreased slightly during the infusion but subsequently returned to normal. More women (59.3%) treated with 400 mg/kg intravenous immuno globulins (IVIG) manifested symptoms compared to 38.5% of women treated with 200 mg/kg IVIG ($p = 0.185$). The only common symptom that appeared was a headache which easily resolved after analgesic therapy.*

Conclusion: *Nurses play a very important role in the implementation of IVIG therapy. These results show that women adhere well to this therapy at FIV Valencia and none of them reported any severe symptoms. Our findings may facilitate the design of future research studies aimed at improving care for infertile women.*

Keywords: Infertility; Nursing Practice; Reproductive Health; Intravenous Immuno Globulins

Introduction

Assisted Reproduction Techniques (ART) are currently one of the most demanded options among women with fertility problems. This has led to the emergence of new professionals group to help women who cannot have children spontaneously. The success of these treatments is rising; however, a group of patients still having problems. Specifically, women diagnosed with Recurrent Pregnancy Loss (RPL), those having lost, not necessarily consecutively, three or more pregnancies spontaneously conceived or via ART before week 20 [1,2]. Including women diagnosed with Repeated Implementation Failure (RIF), following the transfer of two good quality embryos in a minimum of three cycles (a total of six embryos) for women aged under 40, or after the transfer of four good quality embryos in two cycles of egg donation [3,4].

Although RPL and RIF are different clinical entities, the literature shows common defining characteristics, in particular alterations associated with the functioning of the immune system [5-8]. The inflammatory immune response may be altered in women with RPL and/or RIF due to the increase of natural killer cells (NKC) in peripheral blood [5, 9, 10]. Infusion with human intravenous immunoglobulin's (IVIG) is a treatment option either alone or combined with the administration of other immunologic agents as corticoids.

Some authors consider the positive benefits of IVIG therapy in terms of increment in birth rate in women who had suffered two or more spontaneous abortions [11]. IVIG administration has potential benefits in women with RPL and RIF who present NKC increments [12, 13]. Additionally, other papers have explicitly shown that this treatment act as an immuno modulator mechanism which reduces NKC activation and favors embryonic implantation increasing the clinical pregnancy rate in women with RIF [14].

The administration of IVIG in women with autoimmune problems expressed as NKC increase in peripheral blood produces a significant increase in the pregnancy and live birth rates in women with RPL and RIF [15-21]. A meta-analysis noted the importance of screening properly the women candidate to IVIG to select those women diagnosed with RIF and/or RPL that will be beneficed [22]. Stephenson, et al., concluded that IVIG is not benefit in women with idiopathic RPL; and Polanski, et al., justified the need to further research into this type of adjuvant therapy in order to obtain further evidence of efficacy [23, 24]. In any case, different works evaluated the effectiveness of IVIG therapy in relation to the pregnancy and new-born birth rates in women treated with ART [25].

Understanding clinical evolution and the care of women undergoing IVIG therapy forms part of the bio psychosocial approach of ART and nursing where this profession plays a pivotal role in terms of safety and adherence, before, during and the follow-up of the patient. In these cases it was considered to be a safe therapy with no counter-productive effects [18, 19, 20, 21, 26, 27]. To our knowledge, we could not find any research that evaluated the nursing work in the preparation, implementation, and follow-up of infertile women after IVIG administration. In this study, our goal was to understand deeply the technical process and the level of tolerance and adaptation of women receiving IVIG therapy at FIV Valencia (Spain).

Materials and Method

This was a prospective observational study in women undergoing IVIG therapy at FIV Valencia (Spain). Screening for NKC in peripheral blood, specifically CD3-CD56+CD16+ identified as total Natural Killer (total NK), CD3-CD56++ identified as Natural Killer-bright (NK-bright), and CD3+CD56+ identified as Total Natural Killer-like (NKT-like) sub-populations identified 75 women among those already diagnosed with RIF or RPL with fertility problems due to a potential immune response. Any women presenting physiological or pathological processes that could mask the immunological response were excluded, including infectious or inflammatory processes in previous three months, abortion or curettage procedure in the past month, or treated with immunosuppressive therapy. According to previous research the total NKC count should be less than 18%, bright NKC less than 13%, and NKT-like at around 10% [11, 18, 26]. In cases that showed that NKC were within the normal limits, we opted for conservative treatment with corticosteroids. In cases with an apparent NKC population-increase was necessary to check again to confirm the diagnosis.

Once diagnosed, before the first infusion, an evaluation of immunoglobulin's (IgA, IgG and IgM), blood cells and renal and hepatic function was carried out. Then treatment with IVIG was started after obtaining the informed consent. For successive infusions, renal and hepatic function and IgG quantification were requested, in case of alteration a consultation with the immunologist was necessary before making any decision to suspend or adjust the infusion dose. It is important to clarify that several infusions of IVIG can be administered to the same patient during induction and/or maintenance until week 34.

The first IVIG dose referred as induction dose, administered prior to embryo transfer, either on the same day or within a maximum of 24 hours, was of 400 mg/kg. This dose was infused three more times, every three weeks, if the woman became pregnant. From week 14 of pregnancy a half of the initial dose was perfused as maintenance dose (200 mg/kg), which we administered every four weeks until week 34.

The day of initiation of the treatment the patient was admitted with the only recommendation of eat some food before the arrival because the treatment should not be administered with an empty stomach. The nurse checks the patient identity, evaluate the past few days assessing possible incidents, and determine body temperature (CBT) with a digital thermometer. In addition, the nurse checks the diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR) with a digital manometer, establishing a vein cannulation and providing premedication (1 gr. oral paracetamol and 5 mg/ml intravenous dexchlorpheniramine) according with protocol.

After 20-30 minutes, the immunoglobulin infusion (via a perfusion pump) was initiated at the prescribed dose. The infusion rhythm was established depending on the patient's evolution; DBP, SBP, and HR were determined every 30 minutes and the CBT was recorded at the end of the administration dose. In case of an allergic reaction the infusion was reduced or suspended according the doctor. If it was feasible, after achieving the hemodynamic stabilization of the patient, the perfusion was continued at slower pace. All of the data collected including batch of the product infused, was collected by the nursing team at the clinical history.

After 20-30 minutes of observation without problems, the patient discharged. After 48 hours the nurse will check state of the patient using a Likert scale with four levels (excellent, good, regular, and bad) to categorize the responses, and evaluate the occurrence of any adverse effects (chills, headache, dizziness, fever, nausea/vomiting, lower back pain, arthralgia, chest pain, or others), giving advice when necessary. All the data was collected in a database and was statistically analyzed using SPSS (version 23.0). A parametric Student t test was used to monitor the vital signs recorded during the infusions, and the non-parametric chi-squared test to analyze any symptoms which appeared after a cycle of IVIG.

Results

Of all the patients diagnosed with RPL/RIF (total 75) during the screening, 8 had a peripheral blood NKC expansion; 8 patients were treated at the center with a total of 40 IVIG infusions (n = 40). Specifically, in the present study 27 IVIG cycles were induction dose of 400 mg/kg and 13 were single maintenance dose of 200 mg/kg. The infusion protocol was suspended in women that did not achieve pregnancy, miscarried, or had a pre-term delivery. The specific doses were adjusted according to the patient's weight, but in the majority of cases was 25 g, and the minimum infused dose was 22.5 g (Table 1). The initial infusion speeds were 42 ml/h and 50 ml/h depending on whether the doses were in the first or subsequent cycles, respectively.

Table 1: Descriptive data related to IVIG cycles performed at FIV Valencia

Type of IVIG dose	Frequency	Percentage
Induction dose (400 mg/kg)	27	67.5
Maintenance dose (200 mg/kg)	13	32.5
Total	40	100.0
IVIG dose quantity	**Frequency**	**Percentage**
[Induction dose] 25.00 g	22	55.0

[Induction dose]	24.00 g	1	2.5
[Induction dose]	22.50 g	4	10.0
[Maintenance dose]	12.50 g	13	32.5
Total		40	100.0

Source: internal.

During the 40 IVIG infusions the patients were controlled by monitoring DBP, SBP, HR, and CBT by the nurse. In 27 induction IVIG cycles we observed a significant reduction in both the average DBP and SBP during infusion (108.30 mmHg and 67.07 mmHg, respectively), compared to basal state (121.41 mmHg and 73.00 mmHg, respectively; p = 0.000). This parameters returned to basal state when the infusion ended (113.07 mmHg, p = 0.002; and 71.22 mmHg, p = 0.206, respectively). Additionally, the basal average heart rate (81.81 bpm) decreased during infusion, reaching an average of 68.93 bpm (p = 0.000) but recovered initial values after the cycle finished (70.96 bpm, p = 0.000). The CBT also decreased to a statistically significant degree (p = 0.023) in all the cycles (Table 2).

Table 2: Monitoring of vital signs during the induction cycles (27 cycles)

Variable/ Time measuring:	Basal state	During infusion	End of infusion
Average SBP (mmHg)	121.41 ± 9.932	108.30 ± 8.530[1]	113.07 ± 9.021[2,3]
Average DBP mmHg)	73.00 ± 6.251	67.07 ± 6.275[4]	71.22 ± 5.139[5,6]
Average HR (bpm)	81.81 ± 8.526	68.93 ± 6.989[7]	70.96 ± 6.964[8,9]
Average CBT (°C)	36.23 ± 0.476		36.50 ± 0.552[10]

Source: internal. Note. The data are shown with the standard deviation. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CBT: core body temperature; 1p = 0.000 compared to basal; 2p = 0.002 compared to basal SBP; 3p = 0.026 compared to infusion SBP; 4p = 0.000 compared to basal DBP; 5p = 0.206 compared to basal DBP; 6p = 0.002 compared to infusion DBP; 7p = 0.000 compared to basal HR; 8p = 0.000 compared to basal HR; 9p = 0.071 compared to infusion HR; 10p = 0.023 (Student t test).

In the 13 maintenance IVIG dose cycles, the average SBP (117.77 mmHg) and DBP (73.69 mmHg) decreased during infusion being statistically significant (106.62 mmHg and 65.38 mmHg, respectively; p = 0.000) compared to the baseline values (108.38 mmHg, p = 0.001 and 67.77 mmHg, p = 0.008, respectively) but recovered at the end of the therapy. The HR varied in the same way; the average basal HR in these cycles was 83.62 bpm, which decreased to an average of 74.15 bpm during infusion (p = 0.000) and increased again at the end of the cycle (75.46 bpm, p = 0.022). There was no significant change in CBT during the monitoring (Table 3).

Table 3: Vital sign monitoring during the maintenance cycles (13 cycles)

Variable/ Time measuring:	Basal state	During infusion	End of infusion
Average SBP (mmHg)	117.77 ± 8.908	106.62 ± 9.124[1]	108.38 ± 9.305[2,3]
Average DBP (mmHg)	73.69 ± 7.761	65.38 ± 6.252[4]	67.77 ± 5.904[5,6]
Average HR (bpm)	83.62 ± 11.169	74.15 ± 8.601[7]	75.46 ± 10.413[8,9]
Average CBT (°C)	35.89 ± 0.585		36.08 ± 0.468[10]

Source: internal. Note. The data are shown with the standard deviation. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CBT: core body temperature; 1p = 0.000 compared to basal; 2p = 0.001 compared to basal SBP; 3p = 0.304 compared to infusion SBP; 4p = 0.000 compared to basal DBP; 5p = 0.008 compared to basal DBP; 6p = 0.187 compared to infusion DBP; 7p =0.000 compared to basal HR; 8p = 0.022 compared to basal HR; 9p = 0.553 compared to infusion HR; 10p = 0.165 (Student t test).

The administration of IVIG 48 hours later: Home monitoring

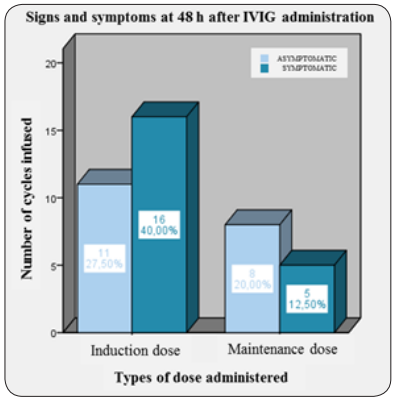
Patients point out their state choosing the maximum level (excellent) of the Likert scale. In 47.5% of cases no adverse reactions were reported, as shown in Table 4. None of the treatments required medical control or follow-up. In figure 1, is presented the occurrence of symptoms in function of induction or maintenance dose. 52.5% (21) of cases were symptomatic, 40% (16) of cases were only symptomatic when infused with the higher dose, i.e. the 400 mg/kg induction dose, and the remaining 12.50% (5) were still symptomatic when administered the maintenance dose (200 mg/kg). The percentage of asymptomatic cases was 27,50% (11), when the induction IVIG dose (400 mg/kg). With the maintenance dose (200mg/kg) it was 20,00% (8).

Table 4: Appearance of symptoms as a function of the IVIG dose administered

		Post-IVIG symptoms (48 h)		Total
		ASYMPTOMATIC	SYMPTOMATIC	
Induction dose (400 mg/Kg)	Frequency	11	16	27
	Percentage	27,5%	40%	67,5%
Maintenance dose (200 mg/Kg)	Frequency	8	5	13
	Percentage	20 %	12.5%*	32,5%
Total	Frequency	19	21	40
	Percentage	47.5%	52.5%	100.0%

Source: internal. Note. * ***p* = 0.185** compared to the percentage in induction dose cycles (chi-squared test)

Figure 1: Distribution of cycles administered as a function of appearance of symptoms with respect to the total (n = 40)



Source: Internal.

A 52.5% (21) of the cases showed symptoms, and the percentage was different in function of the administered dose. 40% (6) of the patients verbally expressed adverse effects 48 hours after the infusion, it was 12,5 % (5) (p = 0.185) with the maintenance dose. Headache was annunciated by all patients and in one isolated case

arthralgia and malaise. The headache was treated with first grade analgesic therapy, with of disappearance symptoms.

Discussion

None of cases had adverse reactions to the immunoglobulin's (including pruritus, fever, chills, hypotension, and pharyngeal constriction, among others). SBP and DBP monitoring yielded values within the normal limits with a slight decrease during the infusion returning to normality. During induction cycles a decrease of SBP was produced because of the high dose of gamma globulin infused, this created a physiological response to the influx of intravascular proteins which caused homeostatic changes. In any case, differences found were not clinical or hemodynamic relevant.

However, from a statistical perspective HR change significantly during IVIG infusion, regardless of specific dose infused; decreasing during the infusion and rose again at the end of the therapy, although it was always within physiological ranges. Although statistically significant, did not have hemodynamic clinical impact. It could understand as the body's response to the intravenous infusion of proteins. Finally, CBT increase slightly without clinical impact. Appeared headache in 52.5% of the cases as adverse effect and it was treated. Patients received analgesic therapy (paracetamol or metamizol), symptoms disappeared in 24-48 hours without major complications. In any case, the patients stated that headache did not interfere in their activities of daily life. Additionally, during the induction dose one patient presented arthralgia may be associated with causes unrelated to the treatment.

The work published by Stricker and Winger indicates the maximum rate of IVIG infusion attainable is 75 ml/h, administering 200 mg/Kg in all cases, the dose, which we referred to as the maintenance dose in our study [16]. Unlike the results we present here, Stricker and Winger reported the appearance of adverse effects during the infusion in 8% of their patients; these signs and symptoms manifested towards the end of the infusion were characterized as cold, nausea, chills, and vomiting [16]. They reported that vital signs remained stable during the infusion, which coincides with our results and headache appeared in 12% of cases shortly after to finish the infusion, but they did not monitor the patient's evolution at 24-48 h after finishing the treatment. In addition, Eger up, et al. in his report about adverse events (AE) call the attention that AE varies widely between trials. The meta-analyses indicate a higher frequency of AEs after IVIG treatment in women with recurrent miscarriages compared with placebo or treatment as usual. The description of AEs included vaginal bleeding, rash, headache, fever, and itching, not necessarily with causal relationship with IVIG intervention [28]. The observational studies reported similar AEs as the randomized trials [16, 29].

Perricone, et al., state that they did not observe adverse reactions during or after the infusions [17]. Other authors suggest that rapid IVIG infusion may cause thromboembolic problems in some cases, arising from the hyper viscosity of the administered solution, especially where there are additional risk factors such as atherosclerotic or thromboembolic diseases [30]. These situations are often much less frequent in patients undergoing ART compared with the general population. However, the possibility of this type of problem can be prevented by the follow up and assessment of the patients by nurses detecting any symptomatology.

Overall, we can say that patient monitoring and tracking by professional nursing staff allowed the tolerance and general status of the women after treatment to be better understood. The follow up of the cases for nurses during or after the therapy proportionate a high level of security and lead us to think that nurses proportionate an adequate compliance and continuity of care and a guaranty of good quality work of the entire interdisciplinary team at the FIV Valencia. Thus, the infusion of patients undergoing IVIG therapies by professional nurses makes this a safe treatment in which any detectable alteration or physiological change can be immediately redirected.

Only a few studies analyzed and described the administration of this therapy, and there is a not specific protocol for this therapy and the follow up of the cases [18, 19, 20, 21, 26, 27, 31].

It should be emphasized that other studies should be carried out with larger populations in order to corroborate our results, not only in terms of the success of IVIG treatment, but also to check the additional safety proportionate by nursing monitoring. In our case, the women were well selected from the diagnostic point of view and nursing care give a security support from the therapeutic perspective; both are key points in the holistic approach towards achieving the patients' ultimate goal: becoming a mother.

Conclusion

The majority of studies fail to describe how the IVIG therapy was carried out. This study demonstrates the safety of, and women's adhesion to, IVIG therapy. The inductions cycles provoked a minimum change of SBP because of physiological response to the influx of intravascular proteins. In any case, differences found were not clinical or hemodynamic relevant. Patients point out their state choosing the maximum level (excellent) of the Likert scale. Finally, patient monitoring and tracking by professional nursing staff allowed the tolerance and general status of the women after treatment to be better understood.

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[i]**FIV Valencia is the name of the enterprise.**