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IgM-enriched Immunoglobulin (Pentaglobin®) Positively Influences the Course of Post-surgical Intra-abdominal Infections*

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Abstract
Background: Polyvalent IgM-enriched intravenous human immunoglobulin (IVIG) preparations are discussed to be beneficial regarding sepsis outcome.
Materials and Methods: Sixty-four patients with abdominal infection were treated with Pentaglobin® or Albumin. Serum levels of endotoxin and chemokines were determined.
Results: Incidence of fever was 19/28 in the pentaglobin and 18/26 in the albumin group, the percentage of days with fever was 34 ± 26 for pentaglobin and 43 ± 25 for albumin (mean ± SD). Procalcitonin levels of the pentaglobin treated patients fell under the upper limit of normal on day six whereas levels of albumin patients remained elevated.
Conclusion: Pentaglobin® has a positive influence on the course of post-surgery intra-abdominal infection.

Key words: Abdominal Infection, Endotoxin, Intravenous Immunoglobulin, Pentaglobin®, Procalcitonin

Introduction

Severe bacterial infection is still one of the most serious complications after abdominal surgery and one of the most common causes for death of patients on intensive care units even despite of modern therapeutic intensive care strategies and optimal antibiotic treatment [1]. If the patient develops shock and multiple organ dysfunction syndromes, the mortality can reach up to 80% [2].

After abdominal surgery, spreading of bacteria from intestine into the abdominal cavity with subsequent release of toxins leads to infections in about 54% (unpublished data). This is additionally worsened by the fact that the surgical intervention itself leads to a depression of the immune system as shown by a reduced immune response of peripheral blood mononuclear cells to phytohemagglutinin [3].

Human IgA- and IgM-enriched immunoglobulin preparations (IVIG) have been investigated in a number of clinical studies with patients developing sepsis, septic shock, multiple organ dysfunction syndrome, heart surgery and further more [4, 5, 6, 7]. The outcome of these trials were partly contradictory in so far as there is a reduction in mortality or not, but an improvement of the clinical situation has been described unanimously, regardless of the results of the statistical analysis. Furthermore, applicated amounts of immunoglobulin varied considerably between 10 g [8] and 60 g [6].

The theoretical concept of the mechanisms of action of IVIG includes the enhancement of serum bactericidal activity due to neutralizing and opsonizing IgG and IgM antibodies as well as stimulation of phagocytosis and neutralization of bacterial endo- and exotoxins [9, 10]. Furthermore, IgG-mediated modification and specific suppression of cytokine release from activated peripheral blood mononuclear cells may contribute its part, too [11, 12], as well as the amount of cytokines contained in the IVIG preparation and synergistic effects with acylureidopenicillines [13].

During infection, various pro- and anti-inflammatory cytokines are released, e.g. TNF-α representing the central mediator of the inflammation cascade [14]. Measurement of their increase or decrease has been shown to correlate with clinical outcome, especially Il-6 in sepsis patients [15]. The same holds true for procalcitonin which has been proven a highly suitable marker for assessment of severity of infections enabling the prediction of sepsis outcome in critically ill patients [16].

The major objective of this study was to verify the effect of pentaglobin® administered in combination with antibiotics during the beginning of intra-abdominal infections after surgery. Further objectives were the assessment of tolerability of pentaglobin® and the influence of this treatment on immunologic parameters.

Patients and Methods

The Ethics Committee of the University of Wuerzburg approved the study protocol and written informed consent was obtained from all patients. The study was

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conducted according to the Guidelines of Good-Clinical-Practice. Inclusion criteria were the need of surgical intervention due to abdominal infection, antibiotic treatment and age between 18 and 80 years. Patients with severe underlying diseases such as peritoneal carcinosis, severe peritonitis and sepsis, patients with known liver damage or lack of IgA, M. Crohn or Colitis ulcerosa were excluded.

Patients were assigned to either Pentaglobin® or Albumin treatment according to the random plan generated with a pseudorandom generator depending on starting numbers (RANDU, IBM Corporation 1969) at IFNS GmbH. Sealed envelopes labelled solely with the patient number were handed out, containing the respective study medication for identification in the case of emergency. All envelopes were returned unopened.

Study Protocol

Within six hours after surgery, 200 ml of Pentaglobin® (IVIgGMA, Biotest Pharma Germany. 100 ml contain 3.8 g IgG, 0.6 g IgM, 0.6 g IgA) or Albumin, respectively, were given via IV-infusion. Additional 1100 ml were applicated the next 66 hours through continuous perfusion, resulting to a total of 1300 ml in 3 days. Clinical examination and withdrawal of blood for determination of IL-6, IL-8, IL-10, TNF-α, sTNF-R1, sTNF-R2, ICAM, endotoxin, endotoxin neutralising capacity (ENC) and laboratory parameters were made daily up to day 8 and every 2nd day until the end of the follow-up period on day 14 or discharge of the patient, respectively. Immunoglobulin IgA, IgM and IgG including subclasses 1-4 were determined before and 24 hours after administration of pentaglobin®/albumin, respectively.

Acute Physiology and Chronic Health Evaluation Score II was evaluated according to Knaus [17]. Additionally, procalcitonin levels were determined in stored blood samples after the end of the study.

Measurement of Plasma Parameters

TNF-α , sTNF-R1, sTNF-R2, IL-6, IL-8, IL-10 and ICAM were determined using the respective MEDGENIX ELISA-Test (Biosource, Brussels, Belgium). For procalcitonin, the LUMItest (BRAHMS Diagnostica, Berlin, Germany) was used, each according to the recommendation of the manufacturer. Endotoxin and endotoxin neutralising capacity were determined using a chromogenic modification of the LAL test as described elsewhere [18]. The following ranges were regarded as normal: TNF-α <20 pg/ml; sTNF-R1 0.3-2.9 ng/ml; IL-6 3.0-8.5 pg/ml; IL-8 0-47 pg/ml; IL-10 0-112 pg/ml; procalcitonin 0.1-0.5 ng/ml, up to 1.0 ng/ml for hospital patients.

Statistics

The incidence and clinical course of fever as well as the duration of stay in hospital between the two treatment groups were compared by Mann-Whitney-U-test. For binomially distributed variables Fisher's Exact Test was used. Analysis was performed, using the SAS software package by IFNS GmbH, Cologne, Germany (Institute for numeric statistics) .A two-tailed $p<0.05$ was considered significant.

Results

A total of sixty-four patients were enrolled into the study. Demographic characteristics of the study population are given in Table 1. 60 were Caucasians; in four patients no information concerning ethnic origin could be obtained. Comedication is given in Table 2. Antibiotic treatment prior to study inclusion was stated in 17 patients of the Pentaglobin® and 13 of the Albumin group, respectively. Regarding clinical findings no differences were observed between both groups although APACHE II-Score was slightly lower for the pentaglobin®-group.

54 patients with infection confirmed by intra-abdominal swab received antibiotics, mostly 2 x 500 mg metronidazole and 3 x 2 g cefotaxim. The whole group, as well as the subgroups with confirmed infection were comparable concerning demographic parameters. Regarding the rate of complications in both study groups, there was no difference either. Data of patients without confirmed infection were excluded from statistical analysis.

The number and severity of adverse events for the treatment groups are tabulated in Table 3. Most adverse events were hypertonia and cardiac sensations such as tachycardia and arrhythmia. None of the severe AEs and deaths was likely to be related to the study medication. Number and severity of adverse events were lower in the Pentaglobin® group.

Table 4 shows incidence and time course of fever for both treatment groups and the duration of stay in hospital. The number of patients developing fever was almost equal whereas the percentage of days with fever was lower in the Pentaglobin® group, the decline of mean body temperature greater (Fig. 1) and the stay in hospital shorter in the pentaglobin®-group, but neither difference was statistically significantly different. Table 5 tabulates the duration of hospital stay in relation to treatment and different APACHE II-Scores. Patients with low or middle APACHE II Score and pentaglobin® medication had a slight benefit compared to the albumin treated patients.

Table 6 shows the relative differences (percental) between the final observation and the day of operation for the mean values of the immunogical parameters (mean ± (SD) median). IL-8 and IL-10 showed a slightly larger decrease in the albumin-group, whereas TNF-α did so in the pentaglobin®-group. Those patients had a greater decrease in endotoxin levels, too. Leukocytes showed a stronger decrease and thrombocytes a stronger increase in the pentaglobin® group compared to the controls.

Stored blood samples of 56 patients (30 of the pentaglobin® and 26 of the albumin group) were used to measure procalcitonin levels. The time course of procalcitonin levels for both treatment groups is displayed in Figure 2. Both curves show a decline during the first five days. Procalcitonin levels of pentaglobin® patients fall below upper limit for hospital patients (1 ng/ml) on day six and show a further decrease in the

Table 1. Demographic characteristics.

	Pentaglobin®	Albumin	Total
Total	31	33	64
Gender	19 male	17 male	36 male
	12 female	16 female	28 female
Age mean (SD)	61±11 (65)	63±11 (66)	62±14 (66)
Bodyweight [kg] mean± SD (median)	71±14 (70)	77±15 (77)	
Height [cm] mean± SD (median)	169±8 (168)	168±8 (169)	
Non-Smoker	21	26	47
Smoker + past Smoker	10	7	17
Cigarettes / Day, mean (SD)	14 (7)	20 (4)	
Infection confirmed	28	26	54
APACHE II mean± SD (median)	9.81± 6.75 (10.0)	10.39± 6.68 (10.0)	
Radiographic findings:			
extra-intestinal air	4	4	8
air-fluid-levels	2	1	3
free air under right diaphragm	1	2	3
Examinational findings:			
abdominal guarding	7	9	16
pain on palpation	4	5	9
rebound tenderness	2	2	4
colic pain	23	26	49
decline of physical status	24	24	48
Duration of Operation [h]			
mean± SD (median)	1.81± 0.82 (1.55)	2.43± 1.58 (2.30)	
Duration of Narcosis [h]			
mean± SD (median)	2.49± 0.98 (2.35)	3.11± 1.78 (2.80)	

Table 2. Concomitant Medication.

	Pentaglobin®	Albumin	Total
Antacids	20	21	41
Analgesics	18	18	36
Plasma substitute	18	17	35
Drugs against common cold	18	16	34
Antithrombotic therapy	13	13	26
Cardiovascular Drugs	10	13	23
Diuretics	9	9	18
Total (n)	28	29	57

Table 2 displays the comedication of the study-patients for both groups. Multiple entries were possible.

Table 3. Adverse events.

	Pentaglobin®	Albumin
Number of patients with AEs	15 (48.4%)	19 (57.6%)
Number of total episodes	20	44
– severe	7	21
– moderate	8	13
– modest	1	0
– unknown	1	0
Number of severe AEs	2	18
Death	1	2

Table 3 lists the adverse Events (AEs) for the treatment groups. All severe AEs and Deaths were unlikely to be related to the study medication.

follow-up period whereas procalcitonin levels of albumin-treated patients re-increase and do not reach the normal range.

Discussion

The amount of patients developing at least one episode of fever was equal in both treatment groups, but regarding the time course of fever, the percentage of days with fever were fewer in the pentaglobin group. Correspondingly, body temperatures decreased in the pentaglobin® group but tended to rise in the placebo patients. Kress et al. [7] has also demonstrated this beneficial effect of IVIG on post-operative body temperature by although their findings did not reach statistical significance either.

Table 4. Incidence and time course of fever.

	Pentaglobin®	Albumin	p+
Incidence of fever, n (%)	19/28 (67.9%)	18/26 (69.2%)	
Percentage of days with fever, mean±SD (median)	34±26 (27)	43±25 (33)	0.2284
Difference of mean temperature [°C], mean±SD* (median)	0.62±1.06 (0.60)	0.11 ±1.58 (0.15)	0.0824
Duration of stay in hospital, mean±SD (median)	21±20 (16)	36±45 (15)	0.3085

*Day of operation vs. last observation; + p-value of Mann-Whitney-U-test

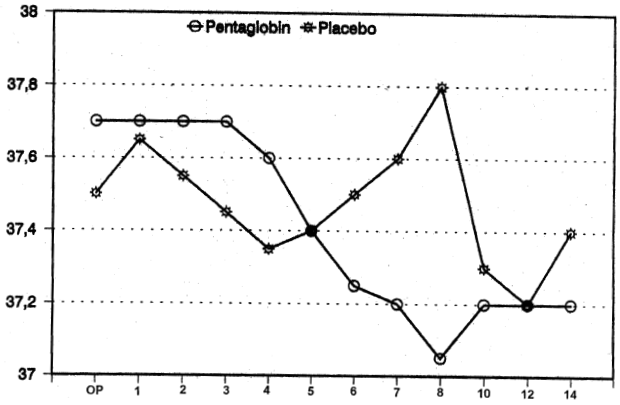

Fig. 1. Time course of body temperature for treatment groups expressed as median °C.

Table 5. Duration of stay in hospital by treatment and APACHE II-Score, mean± SD (median).

APACHE II-Score	Pentaglobin®	Albumin
<11	19 ± 19 (13)	32 ± 48 (15)
11-15	22 ± 14 (18)	55 ± 41 (56)
>15	28 ± 28 (20)	19 ± 16 (13)
total	21 ± 20 (16)	36 ± 45 (15)

The duration of stay in hospital was shorter for patients treated with pentaglobin® compared to those receiving only albumin, as was the duration of mechanical ventilation (data not shown) whereas the difference is not statistically significant. This is due to the large standard deviation resulting from the course of one single patient. Therefore the trend towards an advantage for pentaglobin® might be significant in larger patient groups.

Reduction of the mean duration of stay in hospital as well as on ICU results in a better cost-benefit ratio. This implies the possibility to lower therapy-costs of postoperative infections by routine prophylactic administration of pentaglobin® in combination with antibiotics. Furthermore, a reduction in the incidence of complications and side effects might result in an additional decline in expenses for the appropriate treatment of those complications. Certainly it has to be considered that the therapy of critically ill patients is

Table 6. Differences between last observation and day of operation (%).

Parameter	Pentaglobin®	Albumin
IL-6 [pg/ml]	N = 15 87.96 ± 26.0 (97.84)	N = 10 86.58 ± 18.7 (94.63)
IL-8 [pg/ml]	N = 14 31.61 ± 39.6 (27.1)	N = 10 44.91 ± 65.5 (62.40)
IL-10 [pg/ml]	N = 15 47.55 ± 63.7 (64.29)	N = 10 62.31 ± 30.8 (70.83)
ICAM [pg/ml]	N = 2 –44.13 ± 60.6 (-44.13)	N = 2 2.27 ± 0.0 (2.27)
TNF-α [pg/ml]	N = 14 29.69 ± 26.0 (23.61)	N = 9 8.32 ± 52.4 (16.69)
sTNF-R1 [ng/ml]	N = 15 20.10 ± 74.5 (41.09)	N = 9 27.86 ± 20.4 (32.60)
Leucocytes [1000/µl]	N = 26 –2.9 ± 6.91 (-2.3)	N = 23 –2.5 ± 7.7 (-2.9)
Thrombocytes [1000/µl]	N = 26 144.65 ± 149.2 (175.50)	N = 23 115.57 ± 133.5 (142.00)

Table 6 gives the relative differences (percental) of the immunological parameters between the final observation and the day of operation for the mean ± SD (median) and the number of samples, which were analysable within each parameter and group. Patients without confirmed infection were excluded from analysis.

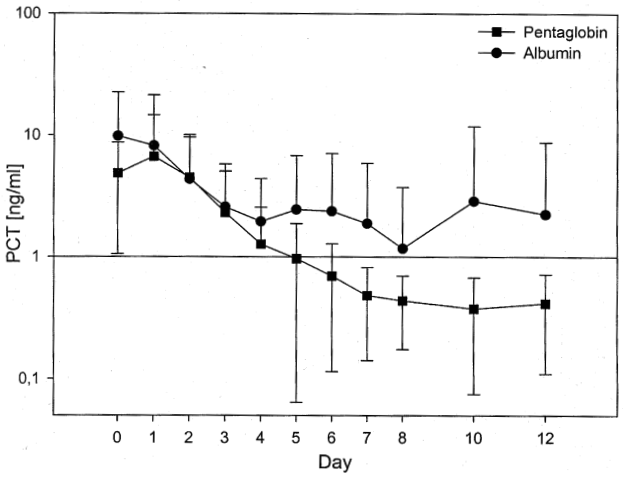

Fig. 2. Levels of procalcitonin over the time expressed as mean ±SD divided by the treatment as a semi logarithmic graph. Procalcitonin levels of the pentaglobin® patients fall below the upper limit of normal of 1 ng/ml on day six whereas those of albumin patients remain elevated.

based on a multiform strategy and the all-in-all economic consideration is the sum of multiple single factors [19].

Levels of TNF-α and endotoxin showed a stronger decrease from the value at the day of operation to last observation, although baseline values of both parameters were higher in the pentaglobin® group. The therapeutical advantage of pentaglobin® compared to placebo could become important remembering the crucial role of TNF-α and endotoxin in the pathogenesis of sepsis. It stresses the potency of pentaglobin® to neutralise endotoxin, and a decrease in endotoxin levels is known to correlate with increased survival [20].

The reduction of IL-8 and IL-10 in the pentaglobin® group was not as pronounced as in the placebo group. This may on the one hand be due to considerable differences of the baseline values between the two groups, limiting their comparability. On the other hand, conflicting results for the correlation between IL-8 and IL-10 levels and the course of infections can be found in the literature. IL-8 is primarily involved in the pathogenesis of pneumonia and is then elevated at the site of infection but not in the contralateral lung or in the blood [21]. Plasma levels increase with generalization of the local infection e.g. in sepsis and septic shock, and are then directly correlated with mortality [22]. The contribution and importance of IL-10 has to be evaluated very critically because of its challenging simultaneous anti-inflammatory and immuno-suppressive properties [reviewed by 23]. The fall in leukocyte counts was greater in the Pentaglobin® group than in the placebo group.

The incidence of complications within the group of pentaglobin® treated patients was lower than in the placebo group. This is consistent with the observation that immunoglobulin preparation administered immediately after cardiac surgery significantly reduced the incidence of postoperative infections [7] and that IVIG given prophylactically to patients on surgical ICUs could reduce post-surgical infections such as nosocomial pneumonia [5; 24].

Three of our patients died, one in the pentaglobin® and two in the albumin group. No conclusion whether there is a benefit can be drawn therefrom, however, this study was not designed for investigating mortality. Data from other studies are somewhat conflicting. A study at our hospital has demonstrated a reduction in mortality from sepsis and septic shock by adjuvant therapy with IVIgGMA [25]. As well, reports of Schedel et al. [6] and Dominioni et al. [26] proved a beneficial effect of IVIG administration in adult sepsis patients. In contrast, some investigations found that IVIG preparations could not reduce mortality in sepsis patients [4, 27]. Hence, Werdan [10] stated that therapy with IVIgGMA preparations should be regarded as one player in a concert of therapeutic strategies contributing to an improvement in the management of severe infection and critically ill patients. The very recent Cochrane Analysis came to the conclusion that polyclonal IVIG significantly reduced mortality and is a promising adjuvant in the therapy of sepsis and septic shock. They also stated that all the clinical trials included in the respective analysis were too small and that the totality of the evidence is insufficient to support a robust conclusion of benefit [28].

For the interpretation of our data it is essential to notice that the population of peritonitis-patients is not homogenous. But on the other hand peritonitis can be considered as a well described severe bacterial infection often ending up in sepsis. By using score systems such as the Mannheim Peritonitis Index (MPI) [29, 30] it is possible to define study populations very meticulously. This score considers the items age, gender, organ failure, malignancy, duration and focus of peritonitis, distribution and exudation and it is possible to predict the outcome of the patients [30] and to compare different patient population precisely.

Most of the encouraging results of IVIgGMA preparations for reduction of mortality have been observed in restricted sepsis subgroups. Supplementary in- and exclusion criteria may lead to well-defined study populations. Exemplarily, for patients in our study who underwent re-laparotomy the benefit of pentaglobin® compared to albumin concerning the parameters IL-6, IL-8, IL-10, TNF-α and sTNF-R1 was much more pronounced than in the whole study group.

In all our patients plasma procalcitonin levels were elevated at the onset of infection according to the known fact that procalcitonin concentrations correlate with severity of infection [31]. Concentrations decreased in both treatment groups until day six, afterwards PCT of pentaglobin® patients fell below the upper limit of normal, whereas PCT of the albumin group re-increased. Interestingly, a very recent investigation found similar conditions in sepsis patients: survivors showed a continuous decline of PCT after the onset of severe sepsis; non-survivors were characterized by permanently elevated serum PCT levels or a re-increase after the first week [32]. They additionally observed an inverse correlation between the proinflammatory reaction represented by the increase in PCT levels and the anti-inflammatory reaction characterized by a monocytic HLA-DR suppression within the first week of sepsis in all patients regardless of outcome. In survivors, HLA-DR expression recovered with decreasing PCT values whereas non-survivors remained immunoparalysed, leading to the conclusion that this inverse relationship is part of an autoregulatory feedback mechanism aimed at limiting the cellular immune response. If their conclusion is true, the time-course of PCT serum concentrations in our study would allow deducing the hypothesis that pentaglobin® is highly effective in improving the clinical course of infection.

Conclusion

The administration of Pentaglobin® has a positive influence on the course of post-surgery intra-abdominal infection demonstrated by a decline in procalcitonin levels, mitigation of fever, reduction of the duration of stay in hospital and the improvement of clinical symptoms, whereas larger studies in well-defined subgroups are still to be conducted to show significance. Pentaglobin® has been proven as a safe and well-tolerable therapy.

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