Intensive Care Med (2017) 43:1585–1593
DOI 10.1007/s00134-017-4786-0

SEVEN-DAY PROFILE PUBLICATION

Immunoglobulin G for patients with necrotising soft tissue infection (INSTINCT): a randomised, blinded, placebo-controlled trial

Martin B. Madsen[1], Peter B. Hjortrup[1], Marco B. Hansen[2], Theis Lange[3,4], Anna Norrby-Teglund[5], Ole Hyldegaard[2] and Anders Perner[1*]

Abstract

Purpose: The aim of the INSTINCT trial was to assess the effect of intravenous polyspecific immunoglobulin G (IVIG) compared with placebo on self-reported physical function in intensive care unit (ICU) patients with necrotising soft tissue infection (NSTI).

Methods: We randomised 100 patients with NSTI 1:1 to masked infusion of 25 g of IVIG (Privigen, CSL Behring) or an equal volume of 0.9% saline once daily for the first 3 days of ICU admission. The primary outcome was the physical component summary (PCS) score of the 36-item short form health survey (SF-36) 6 months after randomisation; patients who had died were given the lowest possible score (zero).

Results: Of the 100 patients randomised, 87 were included in the intention-to-treat analysis of the PCS score, 42 patients (84%) in the IVIG group and 45 patients (90%) in the placebo group. The two intervention groups had similar baseline characteristics with the exception of IVIG use before randomisation (1 dose was allowed) and rates of acute kidney injury. Median PCS scores were 36 (interquartile range 0–43) in the group assigned to IVIG and 31 (0–47) in the group assigned to placebo (mean adjusted difference 1 (95% confidence interval −7 to 10), $p = 0.81$). The result was supported by analyses adjusted for baseline prognostics, those in the per protocol populations, in the subgroups (site of NSTI) and those done post hoc adjusted for IVIG use before randomisation.

Conclusions: In ICU patients with NSTI, we observed no apparent effects of adjuvant IVIG on self-reported physical functioning at 6 months.

Trial registration: NCT02111161.

Keywords: Fournier's gangrene, Necrotising fasciitis, Patient-reported outcome measure, Quality of life, Sepsis, SF-36

Introduction

Necrotising soft tissue infections (NSTI) are characterised by the rapid progression of infection in any layer of the skin and soft tissue, resulting in tissue necrosis, sepsis, high rates of morbidity and mortality, and impaired quality of life among the survivors [1]. The infection may be monomicrobial caused by β-haemolytic streptococci, clostridium species, or *Staphylococcus aureus* or polymicrobial involving a spectrum of anaerobic and aerobic bacteria [2]. The management of these patients includes rapid surgical debridement and broad-spectrum antibiotics [3], and in many centres, adjuvant intravenous polyspecific immunoglobulin G (IVIG) is used [4, 5].

*Correspondence: anders.perner@regionh.dk
[1] Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
Full author information is available at the end of the article

Take-home message: Treatment with adjuvant intravenous polyspecific immunoglobulin G in patients admitted to the intensive care unit with necrotising soft tissue infections did not improve physical quality of life in the randomised, blinded, placebo-controlled INSTINCT trial.

Springer

IVIG inhibits the activity of streptococcal and staphylococcal virulence factors [6–8] and might therefore benefit patients with NSTI. The effects of IVIG vs placebo have been assessed in one randomised trial in patients with streptococcal toxic shock syndrome [9], but the trial was stopped prematurely after the inclusion of only 21 patients as a result of slow patient recruitment. Thus, the evidence base for the use of IVIG comes mainly from retrospective studies [10–15] and case reports. The objective of the INSTINCT trial was to assess the effect of IVIG vs placebo on self-reported physical function in intensive care unit (ICU) patients with NSTI. Patient-reported outcomes are important as they are based on the patient's own perceptions, and patients sense changes in functional status well [16]. Our hypothesis was that adjuvant IVIG would improve physical function by inhibiting bacterial toxins and the inflammatory process and thereby diminishing the affected area and shortening the time of critical illness.

Methods

Trial design

We did a randomised, blinded, placebo-controlled trial at Copenhagen University Hospital, Rigshospitalet, where the management of patients with NSTI in Denmark is centralised. The trial was approved by the Regional Ethics Committee of the Capital Region, Denmark, and the Danish Medicines Agency and was externally monitored by the Good Clinical Practice Unit, Copenhagen University Hospital. The trial was registered with ClinicalTrials.gov, number NCT02111161, before the inclusion of the first patient, and the trial protocol, including the statistical analysis plan, has been published [17].

Patients

We screened all patients with suspected NSTI who were 18 years of age or older. We only included patients with confirmed NSTI at surgical exploration who were admitted to, or planned to be admitted to, the ICU. The diagnosis of NSTI was determined by the surgeon doing the initial operation on the basis of findings such as tissue necrosis, deliquescent tissue and 'dishwater' fluid. We excluded patients who had received more than one dose of IVIG before randomisation, who had had NSTI for more than 48 h, who had known hypersensitivity to IVIG or known hyperprolinaemia, and women who were pregnant or breast-feeding. Informed consent was obtained from two doctors who were independent of the trial before enrolment followed by written informed consent as soon as possible from the patient's next of kin and general practitioner, and the patient.

Randomisation and blinding

Patients were randomised 1:1 to IVIG or placebo. Randomisation was stratified according to the presence or absence of NSTI on either head/neck/extremities to obtain a subgroup with a presumed higher rate of streptococcal or staphylococcal infections [18]. Two allocation lists with variable block sizes of 2, 4 and 6 were computer generated to form two separate boxes that contained sequentially numbered, opaque and sealed envelopes. Patients were randomised by dedicated personnel who drew the next envelope from the box according to the site of NSTI. The randomisation note was handed to an ICU nurse not otherwise involved in the care of the patient who placed both IVIG and 0.9% saline in a black, opaque plastic bag, inserted an orange-coloured infusion set into the allocated intervention (IVIG or saline) and sealed the bag with a plastic strip (more details are given in the Electronic Supplementary Material (ESM)). Patients, clinical staff caring for the patients, research staff, the statistician and the authors when writing the first draft for the abstract (supplementary results in the ESM) were all blinded to the intervention.

Intervention and follow-up

Patients received IVIG (Privigen, CSL Behring, Bern, Switzerland), 25 g/day for three consecutive days, or an equivalent amount of 0.9% saline. The first dose of trial medicine was given immediately after arrival to the ICU or, if appropriate, in the operating room before planned ICU admittance, and in the following 2 days unless the patient had a serious adverse reaction or was discharged from the ICU. All other interventions were given at the discretion of the treating clinicians in accordance with the clinical protocols in place at Copenhagen University Hospital, Rigshospitalet, including those for the treatment of NSTI: repeated surgical revisions, IV antibiotics (meropenem, clindamycin and ciprofloxacin) and three sessions of hyperbaric oxygenation; sepsis, and supportive intensive care. Patients were followed up for 180 days after randomisation using hospital notes, the Danish National Patient Registry and telephone interview.

Outcome measures

The primary outcome was patient-reported physical function as the physical component summary (PCS) score of the Medical Outcomes Study 36-item short form health survey version 2 (SF-36) at day 180 after randomisation. The PCS score ranges from 0 to 100 with a higher score indicating better physical health [19]; its reliability and validity were found to be satisfactory in an ICU setting [20], and it has previously been recommended as a

generic measure in critical care [21]. A printed copy of the Danish SF-36v2 was mailed to the patients, and Martin Bruun Madsen conducted the survey by telephone interview if possible, using the SF-36v2 standard interview script (Danish). The PCS score was calculated using Scoring Software 4.0 (QualityMetric Health Outcomes™, Lincoln, USA).

The secondary outcomes were mortality at 28, 90 and 180 days; time to resolution of shock defined as maintenance of a systolic blood pressure of at least 90 mmHg without vasopressor agents for 24 h [22]; severe bleeding defined as clinical bleeding and use of 3 units of RBC within 24 h of the episode in the ICU after randomisation [23]; any bleeding in the ICU after randomisation; total volumes of blood products used in the ICU after randomisation; sepsis-related organ failure assessment (SOFA) scores at days 1–7 after randomisation, excluding the Glasgow coma scale score [24]; use of renal replacement therapy (RRT), ventilation and vasopressor in the ICU after randomisation; serious adverse reactions observed in the ICU after randomisation; days alive off life support in the 90 days after randomisation; days alive and out of hospital in the 180-day follow-up period; and any amputation (yes/no) within the 180 days.

Statistical analysis

A total of 100 patients were needed to show a 7-point increase (approximately 15% relative increase) in the PCS score of SF-36 at day 180 on the basis of a mean PCS score of 42 (SD 11) in the control group, an alpha of 0.05 and a power of 80%. The values for PCS score and standard deviation were derived from our own follow-up study of patients with NSTI (unpublished). Patients who died before day 180 were given the worst possible PCS score (zero).

The statistician (TL) did the analyses while still blinded to the intervention according to the statistical analysis plan (SAP) (the SAP is available in the ESM) [17]. The primary analysis of the primary outcome was a regression analysis adjusted for the stratification variable (site of NSTI) in the intention-to-treat population. In secondary analyses, the primary outcome was also analysed with adjustments for age and SOFA score at baseline and imputed missing PCS scores, in two per protocol populations, and in the subgroups with and without NSTI of head/neck/extremities. We did a post hoc analysis of the primary outcome adjusted for site of NSTI, age, SOFA score and IVIG use prior to randomisation to estimate the impact of the observed baseline imbalance in IVIG use prior to randomisation. Details of the analyses of the secondary outcomes are described in the statistical analysis plan (ESM). All analyses were performed in R 3.2.1 using mice package 2.25, lme4 package 1.1.12 and in SAS 9.4 (SAS Institute Inc., Cary NC, USA). *P* values less than 0.05 were considered statistically significant.

Results

Patients

From 7 April 2014 to 1 March 2016, 129 patients were screened, of whom 100 were enrolled; 50 patients were assigned to the IVIG group and 50 patients to the placebo group (Fig. 1). The characteristics of the patients at baseline appeared to be similar between the groups, with the exception of acute kidney injury and number of patients who had received IVIG before randomisation (Table 1). Details on microbiological findings and co-interventions are presented in Table 1 and Tables S9–S11 (ESM).

Intervention

The patients received a median of three doses of trial medication (IQR 2–3) in both of the intervention groups; the reasons for receiving less than three doses were withdrawal from intervention (Fig. 1), death or ICU discharge. One patient in the placebo group did not receive any trial medication on the request of surrogates shortly after randomisation. One patient in the placebo group received two doses of IVIG after randomisation on the indication of previous follicular lymphoma and low serum IgG by request of the haematologist.

Primary outcome measure

The interviews were done around day 190 after randomisation in both groups (Table 2), but the SF-36 could not be obtained from 13 patients. We thus included 87 patients (87%) in the primary analysis (Fig. 1; Table 2). In one questionnaire, one item (question) was missing; in all the remaining questionnaires there were no missing items. One patient returned the SF-36 after the data were unblinded and the manuscript was written; data from this patient were not included in the primary or secondary analyses, but included in a post hoc sensitivity analysis.

The median PCS scores were 36 (IQR 0–43) in the patients assigned to IVIG as compared with 31 (IQR 0–47) in the patients assigned to placebo [mean adjusted difference 1 (95% CI −7 to 10), $p = 0.81$; Fig. 2 and Table 3, analysed by regression analysis]. We observed no differences between the two groups in the analyses adjusted for age and SOFA score at baseline (Table S1, ESM), in the analysis with missing PCS scores imputed (Table S1, ESM), in the analyses of the per protocol populations (Table S2, ESM), in the post hoc analyses adjusted for use of IVIG before randomisation with and without baseline age and SOFA score (Table S4, ESM), in the post hoc analyses including the questionnaire received after the data were unblinded (Table S5, ESM) or in the

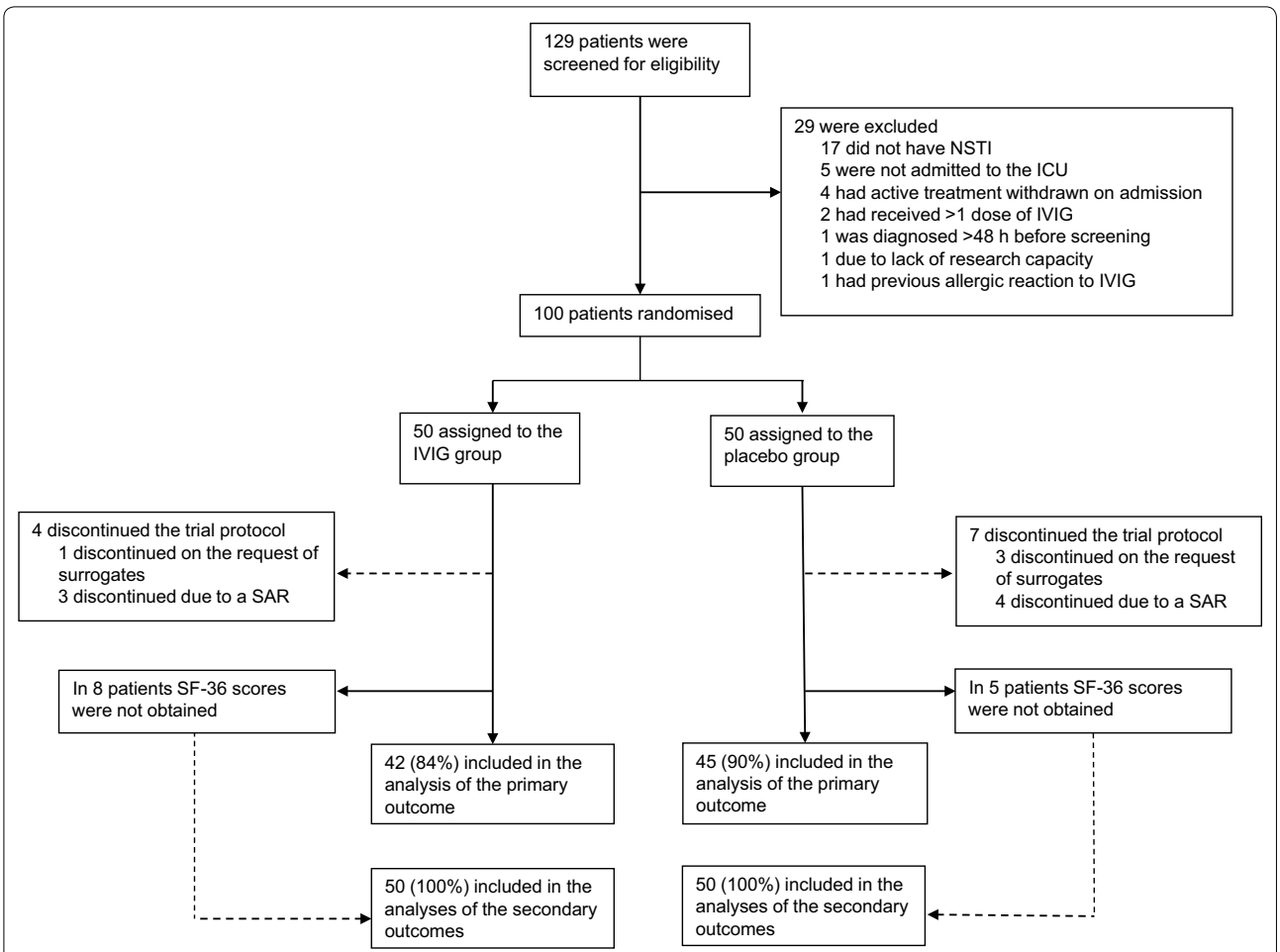


Fig. 1 Flow of trial participants in the INSTINCT trial including screening of patients suspected for NSTI, those not eligible, and those excluded, randomised and followed up. Two patients fulfilled two exclusion criteria. *ICU* intensive care unit, *IVIG* intravenous immunoglobulin G, *NSTI* necrotising soft tissue infection, *SAR* serious adverse reaction

subgroups of patients with and without NSTI of head/neck/extremities (Fig. 2 and Table S3, ESM). The details of the SF-36 scores in the 180-day survivors are presented in Table S8 in the ESM.

Secondary outcome measures

For the secondary outcomes, 100% follow-up was achieved for nearly all outcomes (Table 3). No statistically significant differences between the intervention groups were observed in any of the secondary outcomes (Table 3; Fig. 3).

Discussion

In this randomised, blinded, placebo-controlled trial we observed no difference in physical quality of life at 180 days between patients with NSTI allocated to three doses of IVIG and those receiving three doses of placebo. Also, we observed no statistically significant differences in mortality, organ failures, use of life support or rates of serious adverse reactions between the two groups. This is in line with a recent observational study comparing 322 patients with NSTI using propensity score matched analyses [14].

We chose a difference of 7 points in PCS score as a relevant difference between the two intervention groups. It is not clear what the minimal important difference in PCS score in survivors of NSTI is. In randomised controlled trials (RCTs) in patients with sepsis, minimal important differences of 5 and 8 in mental component summary (MCS) score and PCS score have been used [25, 26], and a similar difference was found in the MCS score between the two intervention groups in the 6S trial [27]. In less severe disease states smaller differences have been suggested to be important [19]. To account for death we

Table 1 Baseline characteristics and microbiological findings

	IVIG group ($n = 50$)	Placebo group ($n = 50$)
Age, years	59 (50–69)	61 (50–71)
Male gender	30 (60%)	32 (64%)
BMI, kg/m^2	26.1 (23.6–33.6)	27.7 (24.7–31.3)
Comorbidities[a]		
Diabetes (type I or II)	13 (27%)	14 (28%)
Chronic liver disease	0	4 (8%)
Chronic kidney disease	2 (4%)	2 (4%)
Haematological malignancy	2 (4%)	3 (6%)
Other active malignancy	2 (4%)	2 (4%)
Where was the patient primarily admitted from		
Home	47 (94%)	46 (92%)
Nursing home	1 (2%)	2 (4%)
Rehabilitation facility	2 (4%)	1 (2%)
Unknown	0	1 (2%)
Site of NSTI		
Extremities/head/neck	26 (52%)	26 (52%)
Other anatomical site	24 (48%)	24 (48%)
SAPS II[b]	43 (34–54)	42 (33–54)
SOFA score[c]	8 (5–10)	7 (4–9)
Septic shock[d]	20 (41%)	18 (40%)
Mechanical ventilation[e]	48 (96%)	47 (94%)
Acute kidney injury[f]	5 (10%)	1 (2%)
Time from admission to primary operation, hours[g]	18 (6–40)	25 (6–50)
Time from primary operation to randomisation, hours	7 (5–10)	7 (6–10)
IVIG before randomisation[h]	8 (16%)	20 (40%)
Microbiological findings		
Polymicrobial infection[i]	31/47 (66%)	31/44 (70%)
Group A streptococcus	4/31 (13%)	1/31 (3%)
S. aureus	5/31 (16%)	3/31 (10%)
Other aerobic bacteria[j]	29/31 (94%)	31/31 (100%)
Anaerobic bacteria[k]	18/31 (58%)	20/31 (65%)
Fungi	4/31 (13%)	3/31 (10%)
Monomicrobial infection[i]	16/47 (34%)	13/44 (30%)
Group A streptococcus	9/16 (56%)	4/13 (31%)
S. aureus	0	3/13 (23%)
Other aerobic bacteria[j]	6/16 (38%)	4/13 (31%)
Anaerobic bacteria[k]	1/16 (6%)	2/13 (15%)
Fungi	0	0

Data are median (IQR), *n* (%) or number of patients/total number in the group (%). The values for the SAPS II, SOFA score, septic shock, acute kidney injury and mechanical ventilation pertain to the 24 h before randomisation. Microbiological results were obtained from tissue samples or blood cultures drawn within 48 h after onset of diagnosis

BMI body mass index, *IVIG* intravenous immunoglobulin G, *SAPS* simplified acute physiology score, *SOFA* sepsis-related organ failure assessment

[a] Chronic liver and kidney disease were defined as described in the patient files. Active malignancy was defined as malignancy other than haematological, and that had not been eradicated. Data on comorbidities are missing for one patient in the IVIG group

[b] SAPS II is calculated from 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease. Data regarding one of the 17 variables were missing for one patient in the group assigned to placebo. The score for this patient is not included here

[c] The SOFA score includes subscores ranging from 0 to 4 for each of five components (circulation, lungs, liver, kidneys and coagulation). Aggregated scores range from 0 to 20, with higher scores indicating more severe organ failure. The scoring was modified because cerebral failure was not assessed. One subscore was missing for one patient in the group assigned to placebo; the score is not included here

[d] Septic shock at randomisation was defined as the need for ongoing vasopressor or inotropic agents in the 24 h before randomisation and a lactate level of 2 mmol/L or above [35]. Data regarding vasopressor agents, inotropic agents or lactate were missing for five patients in the group assigned to placebo and one patient in the group assigned to IVIG

[e] Invasive or continuous non-invasive ventilation

[f] Acute kidney injury was defined as KDIGO stage 3 [36]

[g] Time from admission of the hospitalisation where NSTI was diagnosed, including admissions originally for other reasons

[h] No patients received more than one dose of 25 g

[i] For IVIG group, $n = 3$ without positive microbiology. For placebo group, $n = 6$ without positive microbiology

[j] Other aerobic bacteria include streptococci other than group A streptococcus, staphylococci other than *S. aureus*, enterococci, gram positive cocci other than streptococci, staphylococci or enterococci, enterobacteriacae, gram negative cocci, and vibrio species

[k] Anaerobic bacteria include clostridium species, bacteroides species, fusobacterium, mycobacterium or any other bacteria classified as anaerobic

Table 2 Administration of the SF-36 questionnaire

	IVIG group	Placebo group
Completeness		
Completed questionnaires	31/50 (62%)	31/50 (62%)
Questionnaires not completed	19/50 (38%)	19/50 (38%)
Death	11/50 (22%)	14/50 (28%)
Missing	8/50 (16%)	5/50 (10%)
Time of questionnaire completion, days after randomisation	190 (182–198)	192 (183–200)
Questionnaire administration mode		
Telephone interview	30/31 (97%)	27/31 (87%)
Face-to-face interview	1/31 (3%)	2/31 (6%)
Self-administration	0/31	2/31 (6%)

Data are number of patients/total number in the group (%) or median (IQR)

SF-36 36-item short form health survey

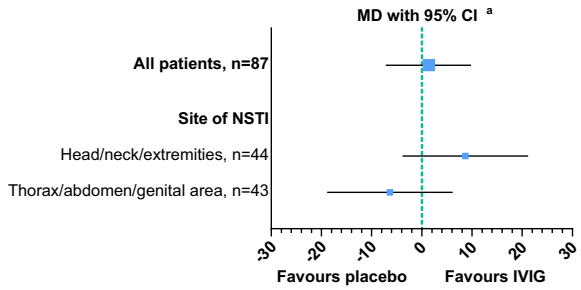


Fig. 2 Mean difference in PCS scores between patients who received IVIG and placebo in the intention-to-treat population, in the subgroup of patients with presentation of NSTI on head, neck or extremities, and in the subgroup of patients with presentation of NSTI on thorax, abdomen or genital area. The individual *points* denote the estimated mean difference between groups and the *lines* on each side the 95% confidence intervals. The *p* value for test of interaction between the two subgroups was 0.08. [a]For all patients the mean was adjusted for site of infection. *CI* confidence interval, *IVIG* intravenous immunoglobulin G, *MD* mean difference, *NSTI* necrotising soft tissue infection, *PCS* physical component summary

gave patients dying before the SF-36 follow-up a PCS score of zero [28, 29]. Using a composite outcome measure may complicate the interpretation of our results [30], but we found it important that death was accounted for in the primary outcome, because it occurs frequently in patients with NSTI.

In vitro and in vivo studies have shown that IVIG can neutralise streptococcal and staphylococcal superantigens [6, 7] as well as the staphylococcal pore-forming toxins [31]. Because the microbiological agent may not be established on ICU admission in all cases, we stratified randomisation on the basis of NSTI of head/neck/extremities to obtain a subgroup with a presumed higher rate of streptococcal or staphylococcal infections. We did not observe statistically significant interaction between the two subgroups and the intervention effect on PCS scores; however, the power of this subgroup analysis was low and the proportion of patients infected with either group A streptococcus or *S. aureus* seemed to be unevenly distributed between the two intervention groups (Table S10, ESM). Interestingly, an RCT on IVIG versus placebo in children with streptococcal toxic shock syndrome has been planned [32].

There are still unresolved issues regarding the use of IVIG in NSTI, including the lack of consensus on the optimal dosage. We used a fixed dose of IVIG of 25 g/day for 3 days, which is lower than the doses used in the previous RCT [9]. In three observational studies, doses varied from 0.2 to 2 g/kg [10–12]; our dose was within this range. However, we cannot exclude that a higher dose would increase efficacy of IVIG. We allowed one dose of IVIG before randomisation because we did not have reason to believe that one dose would be as efficient as three doses, and to ensure that the trial could be completed. Almost all patients received clindamycin. Owing to the ability of clindamycin to inhibit streptococcal virulence factors [33], one could speculate that the addition of IVIG might not add beneficial effect. The timing of administration may also be of importance. In our study, patients were randomised at a median of 7 h from the start of the surgical procedure where NSTI was diagnosed, which was most often performed at the referring hospital.

Our trial has limitations. We had missing data for the primary outcome in 13 patients and the distribution of the data was wider than assumed when we did the sample size calculation, because of our decision to include the dead with a score of zero in the dataset; these two factors reduced the power of the trial. We observed imbalances regarding the number of patients who had received IVIG and who had kidney impairment before randomisation. These imbalances were likely due to chance. In the

Table 3 Primary and secondary outcomes

Primary outcome	**IVIG group**	**Placebo group**	**Mean difference (95% CI)[a]**	***P* value**
PCS score adjusted for site of infection[b]	36 (0 to 43) [29]	31 (0 to 47) [28]	1 (-7 to 10)	0.81[c]
Secondary outcomes	**IVIG group**	**Placebo group**	**Relative risk (95% CI)**	***P* value**
Mortality				
Mortality, day 28	6/50 (12%)	6/50 (12%)	1.00 (0.35 to 2.89)	>0.99
Mortality, day 90	9/50 (18%)	11/50 (22%)	0.82 (0.37 to 1.80)	0.80
Mortality, day 180[d]	11/49 (22%)	14/50 (28%)	0.80 (0.40 to 1.59)	0.65
Serious adverse reactions in the ICU				
All serious adverse reactions[e]	8/50 (16%)	11/50 (22%)	0.72 (0.32 to 1.65)	0.61
Acute kidney injury	6/45 (13%)	8/49 (16%)	0.82 (0.31 to 2.17)	0.78
Thrombi	2/50 (4%)	3/50 (6%)	0.67 (0.12 to 3.82)	>0.99
Use of life-support in the ICU				
Mechanical ventilation	49/50 (98%)	50/50 (100%)	0.98 (0.94 to 1.02)	>0.99
Vasopressor/inotrope	46/50 (92%)	47/50(94%)	0.98 (0.88 to 1.09)	>0.99
Renal replacement therapy	11/50 (22%)	6/50 (12%)	1.83 (0.73 to 4.57)	0.29
Bleeding and amputation				
Any bleeding in the ICU	5/50 (10%)	5/50 (10%)	1.00 (0.31 to 3.24)	>0.99
Severe bleeding in the ICU	4/50 (8%)	2/50 (4%)	2.00 (0.38 to 10.43)	0.68
Amputation in the 180 days after randomisation	4/50 (8%)	6/50 (12%)	0.67 (0.20 to 2.22)	0.74
Secondary outcomes continued	**IVIG group**	**Placebo group**	**Mean difference (95% CI)**	**P value**
SOFA score day 1 to 7[f]	NA	NA	0.15 (-1.70 to 2.00)	0.90[g]
Blood products given in the ICU, ml	1529 (498 to 2559)	1712 (681 to 2742)	-183 (-1641 to 1275)	0.80
Time to resolution of shock in the 28 days after randomisation, days[h]	8.4 (6.1 to 10.8)	8.7 (6.4 to 11.1)	NA	0.69
Alive and off life-support in the 90 days after randomisation, days	70 (61 to 79)	67 (59 to 76)	NA	0.41
Alive and out of hospital in the 180 days after randomisation, days[i]	107 (90 to 124)	99 (82 to 117)	NA	0.50

Data are medians (IQR) [estimated means], number of patients / total number in the group (%) or means (95% CI)

CI confidence interval, *GCS* Glasgow Coma Scale, *ICU* intensive care unit, *IVIG* intravenous immunoglobulin G, *NA* not applicable, *PCS* physical component summary, *SOFA* sepsis-related organ failure assessment

[a] Estimated mean of the IVIG group minus estimated mean of the placebo group as assessed by regression analysis adjusted for site of NSTI

[b] Patients who had died at day 180 were given a PCS score of 0 (zero). We had missing scores for 8 patients in the IVIG group and 5 in the placebo group

[c] Due to deviations from the normality of the residuals, the two groups were also compared by the non-parametric Wilcoxon rank sum test, which also gave a *p* value 0.81

[d] One patient was lost to follow-up before day 180. The patient was a foreign citizen and had left the country

[e] Serious adverse reactions included acute kidney injury, allergic reactions, aseptic meningitis syndrome, haemolytic anaemia, thrombi, and transmittable agents. For the definitions see reference [17]. The total group numbers were below 50 patients for one reaction because 6 patients had this (acute kidney injury) already at baseline

[f] SOFA score excluding the GCS score. The analysis was a repeated measures mixed model. If a patient was discharged before day 7, the best possible SOFA score was given (0), if a patient died before day 7, the worst possible SOFA score was given (20)

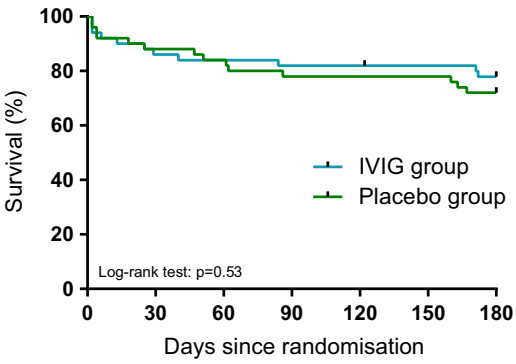
[g] *P* value for likelihood ratio test

[h] Maintenance of a systolic blood pressure $\geq$ 90 mmHg without vasopressor support for 24 hours as previously defined [22]. Patients still in shock at day 28 were given a value of 28. The planned Cox proportional hazards model was replaced by Welch two-sample t-test

[i] We did not have full hospitalisation data for 3 patients up till day 180; all these were foreign citizens

pre-planned analyses adjusted for organ failures at baseline and in the post hoc analyses adjusted for use of IVIG, the point estimates were close to those of the primary analysis of the differences in PCS scores. There is, however, a possibility that the distribution of IVIG received before randomisation could have diluted a potential effect, thereby introducing a type II error. The results of these secondary analyses should be interpreted with caution because we did several analyses and adjustments and some were done post hoc. Also, the trial was performed at one centre only, which reduces the generalisability of the results. We did not measure immunoglobulin levels in plasma, nor did we test the plasma from the patients for antigens or exotoxins to identify subgroups in which IVIG may have had more pronounced effect.

The strengths of our trial include low risk of bias as group allocation was concealed to patients, clinical and research staff, the statistician and the authors when



Numbers at risk

IVIG group:	50	42	38
Placebo group:	50	40	36

Fig. 3 Kaplan–Meier plot for the probability of survival in the intention-to-treat population for the two intervention groups; data were censored at day 180. One patient in the IVIG group was lost to follow-up at day 122. The *p* value given is of the log-rank test; this test was not predefined. *IVIG* intravenous immunoglobulin G

writing the first draft for the abstract, and we adhered to our predefined statistical analysis plan. We obtained acceptable follow-up rates and used multiple imputation of the missing data [34]. Our trial is the first to be completed on IVIG vs placebo in patients with NSTI, the first to systematically collect data on serious adverse reactions, and the first in patients with NSTI assessing a patient-reported outcome measure.

In conclusion, we observed no statistically significant differences in physical quality of life or any of the secondary outcome measures between groups of patients with NSTI allocated to IVIG or placebo in this single-centre, randomised, blinded trial. Large-scale trials are needed to determine whether IVIG should be included in the management of these patients, in particular in subgroups of patients with suspected or confirmed streptococci or staphylococci infection or those with low plasma levels of immunoglobulins.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-017-4786-0) contains supplementary material, which is available to authorized users.

Author details

[1] Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. [2] Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. [3] Department of Public Health, Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark. [4] Centre for Statistical Science, Peking University, Beijing, China. [5] Centre for Infectious Medicine, Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden.

Acknowledgements

We are grateful to the doctors and nurses at Copenhagen University Hospital, Rigshospitalet, to the research staff at the ICU and to the INFECT team for their important contributions and to patients and relatives for their consent to participate.

Compliance with ethical standards

Conflicts of interest

The INSTINCT trial was supported by CSL Behring in the form of trial medication and a research grant for trial conduct, a research nurse and the statistical analyses. CSL Behring had no role in study design, data collection, analysis or interpretation, or writing of the report. MBM and AP conceived the idea and wrote the trial protocol. The trial group has no obligations to CSL Behring, and none of the authors have affiliations to or receive honoraria or funds from CSL Behring. The trial is part of the INFECT project (NCT01790698), supported by the European Union's Seventh Framework Programme.The Department of Intensive Care, Rigshospitalet, receives research funds from Fresenius Kabi, Germany, and Ferring Pharmaceuticals, Denmark.

Received: 9 February 2017 Accepted: 30 March 2017
Published online: 18 April 2017

References

1. Hakkarainen TW, Burkette Ikebata N, Bulger E, Evans HL (2014) Moving beyond survival as a measure of success: understanding the patient experience of necrotizing soft-tissue infections. J Surg Res 192:143–149
2. Hansen MB, Rasmussen LS, Garred P et al (2016) Pentraxin-3 as a marker of disease severity and risk of death in patients with necrotizing soft tissue infections: a nationwide, prospective, observational study. Crit Care 20:40
3. Eckmann C (2016) The importance of source control in the management of severe skin and soft tissue infections. Curr Opin Infect Dis 29:139–144
4. Valiquette L, Low DE, Chow R, McGeer AJ (2006) A survey of physician's attitudes regarding management of severe group A streptococcal infections. Scand J Infect Dis 38:977–982
5. de Prost N, Sbidian E, Chosidow O et al (2015) Management of necrotizing soft tissue infections in the intensive care unit: results of an international survey. Intensive Care Med 41:1506–1508
6. Takei S, Arora YK, Walker SM (1993) Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigens [see comment]. J Clin Invest 91:602–607
7. Norrby-Teglund A, Kaul R, DE Low et al (1996) Plasma from patients with severe invasive group A streptococcal infections treated with normal polyspecific IgG inhibits streptococcal superantigen-induced T cell proliferation and cytokine production. J Immunol 156:3057–3064
8. Sriskandan S, Ferguson M, Elliot V et al (2006) Human intravenous immunoglobulin for experimental streptococcal toxic shock: bacterial clearance and modulation of inflammation. J Antimicrob Chemother 58:117–124
9. Darenberg J, Ihendyane N, Sjölin J et al (2003) Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis 37:333–340
10. Kaul R, McGeer A, Norrby-Teglund A et al (1999) Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome–a comparative observational study. The Canadian Streptococcal Study Group. Clin Infect Dis 28:800–807
11. Mehta S, McGeer A, Low DE et al (2006) Morbidity and mortality of patients with invasive group A streptococcal infections admitted to the ICU. Chest 130:1679–1686
12. Linnér A, Darenberg J, Sjölin J et al (2014) Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin Infect Dis 59:851–857
13. Carapetis JR, Jacoby P, Carville K et al (2014) Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. Clin Infect Dis 59:358–365
14. Kadri SS, Swihart BJ, Bonne SL et al (2017) Impact of intravenous immunoglobulin on survival in necrotizing fasciitis with vasopressor-dependent shock: a propensity-score matched analysis from 130 US hospitals. Clin Infect Dis 64:877–885
15. Cavazzuti I, Serafini G, Busani S et al (2014) Early therapy with IgM-enriched polyclonal immunoglobulin in patients with septic shock. Intensive Care Med 40:1888–1896

16. Basch E (2010) The missing voice of patients in drug-safety reporting. N Engl J Med 362:865–869
17. Madsen MB, Lange T, Hjortrup PB, Perner A (2016) Immunoglobulin for necrotising soft tissue infections (INSTINCT): protocol for a randomised trial. Dan Med J 63:A5250
18. Brook I, Frazier EH (1995) Clinical and microbiological features of necrotizing fasciitis. J Clin Microbiol 33:2382–2387
19. Maurish ME (2011) User's manual for the SF-36v2 health survey, 3rd edn. Quality Metric, Lincoln
20. Chrispin PS, Scotton H, Rogers J et al (1997) Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. Anaesthesia 52:15–23
21. Black NA, Jenkinson C, Hayes JA et al (2001) Review of outcome measures used in adult critical care. Crit Care Med 29:2119–2124
22. Sprung CL, Annane D, Keh D et al (2008) Hydrocortisone therapy for patients with septic shock. N Engl J Med 358:111–124
23. Haase N, Wetterslev J, Winkel P, Perner A (2013) Bleeding and risk of death with hydroxyethyl starch in severe sepsis: post hoc analyses of a randomized clinical trial. Intensive Care Med 39:2126–2134
24. Perner A, Haase N, Guttormsen AB et al (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 367:124–134
25. Schmidt K, Worrack S, Von Korff M et al (2016) Effect of a primary care management intervention on mental health-related quality of life among survivors of sepsis: a randomized clinical trial. JAMA 315:2703–2711
26. Paratz JD, Kenardy J, Mitchell G et al (2014) IMPOSE (IMProving Outcomes after Sepsis)-the effect of a multidisciplinary follow-up service on health-related quality of life in patients postsepsis syndromes-a double-blinded randomised controlled trial: protocol. BMJ Open 4:e004966
27. Wittbrodt P, Haase N, Butowska D et al (2013) Quality of life and pruritus in patients with severe sepsis resuscitated with hydroxyethyl starch long-term follow-up of a randomised trial. Crit Care 17:R58
28. Diehr P, Patrick DL, Spertus J et al (2001) Transforming self-rated health and the SF-36 scales to include death and improve interpretability. Med Care 39:670–680
29. Rygård SL, Holst LB, Wetterslev J et al (2016) Long-term outcomes in patients with septic shock transfused at a lower versus a higher haemoglobin threshold: the TRISS randomised, multicentre clinical trial. Intensive Care Med 42:1685–1694
30. Montori VM, Permanyer-Miralda G, Ferreira-González I et al (2005) Validity of composite end points in clinical trials. BMJ 330:594–596
31. Diep BA, Le VTM, Badiou C et al (2016) IVIG-mediated protection against necrotizing pneumonia caused by MRSA. Sci Transl Med 8:357ra124
32. ClinicalTrials.gov (2016) Effectiveness of intravenous immunoglobulins (IVIG) in toxic shock syndromes in children. https://clinicaltrials.gov/ct2/show/NCT02899702?term=NCT02899702&rank=1. Accessed 23 Nov 2016
33. Goscinski G, Tano E, Thulin P et al (2006) Release of SpeA from Streptococcus pyogenes after exposure to penicillin: dependency on dose and inhibition by clindamycin. Scand J Infect Dis 38:983–987
34. Chevret S, Seaman S, Resche-Rigon M (2015) Multiple imputation: a mature approach to dealing with missing data. Intensive Care Med 41:348–350
35. Singer M, Deutschman CS, Seymour CW et al (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:801
36. Kellum JA, Lameire N (2013) Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 17:204