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ORIGINAL PAPER

Adjunctive homeopathic treatment in patients with severe sepsis: a randomized, double-blind, placebo-controlled trial in an intensive care unit

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***Background*: Mortality in patients with severe sepsis remains high despite the development of several therapeutic strategies. The aim of this randomized, double-blind, placebo-controlled trial was to evaluate whether homeopathy is able to influence long-term outcome in critically ill patients suffering from severe sepsis.**

***Methods*: Seventy patients with severe sepsis received homeopathic treatment ($n = 35$) or placebo ($n = 35$). Five globules in a potency of 200c were given at 12 h interval during the stay at the intensive care unit. Survival after a 30 and 180 days was recorded.**

***Results*: Three patients (2 homeopathy, 1 placebo) were excluded from the analyses because of incomplete data. All these patients survived. Baseline characteristics including age, sex, BMI, prior conditions, APACHE II score, signs of sepsis, number of organ failures, need for mechanical ventilation, need for vasopressors or veno-venous hemofiltration, and laboratory parameters were not significantly different between groups. On day 30, there was non-statistically significantly trend of survival in favour of homeopathy (verum 81.8%, placebo 67.7%, $P = 0.19$). On day 180, survival was statistically significantly higher with verum homeopathy (75.8% *vs* 50.0%, $P = 0.043$). No adverse effects were observed.**

***Conclusions*: Our data suggest that homeopathic treatment may be an useful additional therapeutic measure with a long-term benefit for severely septic patients admitted to the intensive care unit. A constraint to wider application of this method is the limited number of trained homeopaths.** *Homeopathy* **(2005) 94, 75–80.**

Keywords: APACHE II; homeopathy; critically ill patients; intensive care unit; sepsis; survival; double-blind; randomized prospective; placebo-controlled study

Introduction

The incidence of severe sepsis is 70,000 to 300,000 patients in the United States each year.[1] Septic shock is associated with mortality rates ranging from 40% to 90%.[2] Several new therapeutic approaches have failed during the last decades. Recent guidelines[1] recommend use of goal directed therapy, low-tidal ventilation, administration of recombinant Protein C (aPC), close monitoring of blood glucose with a target value of 80–100 mg/dl, and administration of hydrocortisone. Despite these therapeutic strategies, mortality has remained almost unchanged during the last few years.

Homeopathic medicine has been used for about two centuries. Several studies describe its superiority above placebo.[3–5] Experimental studies demonstrate the

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effect of high dilutions[6,7] even beyond Avogadro's number.[7] There are several case reports on the beneficial effect of homeopathy in critically ill patients.[8] We initiated this study to investigate the effect of homeopathy on the outcome of critically ill patients. The aim of this prospective, randomized, double-blind, placebo-controlled trial was to evaluate at two time points (30 and 180 days) whether homeopathy can influence outcome in patients suffering from severe sepsis.

Materials and methods

Patients

The Ethical Committee of the University of Vienna approved the study. Seventy patients admitted to a Medical Intensive Care Unit (MICU) of the University of Vienna were assessed for eligibility, all were included in the study. All were randomized and treated, three had to be excluded because of incomplete data, all of the latter survived. Written informed consent was obtained from all participants or their authorized representatives. The criteria for severe sepsis of Bone *et al.* were used.[9] Patients with a known or suspected infection on the basis of clinical data at the time of screening and three or more signs of systemic inflammation (temperature ≤ 36 or ≥ 38 °C, respiratory rate ≥ 20/min, heart rate ≥ 90/min, leukocytes $\leq 4 \geq 12$ G/L) and sepsis-induced dysfunction of at least two organ systems that lasted no longer than 48 h were included. Treatment with homeopathy or placebo started within 48 h after the patients met the inclusion criteria (Figure 1).

Randomization process

Within 24 h after meeting the criteria for sepsis, all eligible patients were sequentially randomized into two groups, receiving either the homeopathic medicine or placebo, according to a computer-generated code provided by a member of the Department of Medical Computer Sciences. An independent physician not involved into the study held the code. A person not involved in the decision and/or application process for the study prepared the medication for each patient.

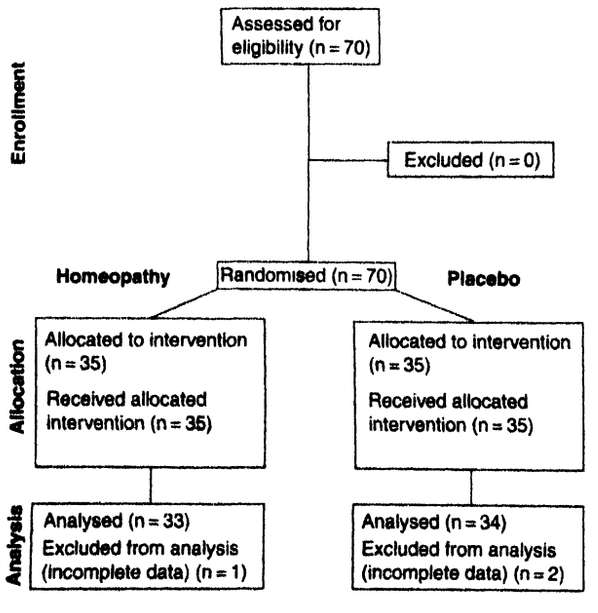

Figure 1. Flow of patients through the study.

Start of therapy and sublingual administration of the globules

Within 12 h after meeting the criteria for sepsis, homeopathic treatment started. A person not involved in the randomization process poured five globules into the lid of the tube containing the globules, then the globules were poured from the lid directly underneath the patient's tongue. In patients with endotracheal tubes, the globules were administered just aside the endotracheal tube. Globules were given twice daily at an interval of 12 h until sepsis was resolved or until death. Patients were treated for the duration of their stay in the intensive care unit. Treatment stopped on transfer to the general ward. Fifteen minutes before and after administration of the globules, no oral fluid or food intake or oral hygiene was allowed to avoid any potential interference with the globules. The homeopathic doctors were free to decide which homeopathic medicine should be applied. All medicines were prepared as a 200c (Rote Krebs Apotheke, Vienna, Austria).

Evaluation of patients

Patients were followed for 180 days after the start of treatment unless death occurred earlier. Base-line characteristics including demographic information and information on pre-existing conditions, organ function, markers of disease severity (APACHE II),[10] and infection were assessed within the 24 h before starting treatment. Adverse effects were recorded during the treatment period.

Statistical analysis

The evaluated end point was death within 180 days. Statistical analysis was done at the Department of Medical Computer Sciences, University of Vienna, using the SAS software package (Statistical Analysis System, SAS Institute Inc., Cary, NC). All statistical analyses were done before breaking the randomization code. Statistical analysis of the data was performed using Kruskal–Wallis Test for comparing the two groups.

Results

No adverse effects were observed in either group. Baseline demographic characteristics including age, sex, weight, height, and body mass index (BMI) as well as prior conditions were similar between the two

groups (Table 1). Baseline clinical indices including APACHE II score and signs of inflammation, the number of organ failures, the need for mechanical ventilation, vasopressor support, veno-venous pump-driven haemofiltration and positive blood cultures were not significantly different between groups. Only heart rate exceeding 90 beats/min differed significantly, occurring more frequently in the placebo group ($P = 0.033$; Table 2).

On day 30, survival showed a non-statistically significant trend in favour of homeopathy (verum 81.8%, placebo 67.7%, $P = 0.19$; Table 3). On day 180, survival was statistically significantly higher in the verum group 1 (verum 75.8%, placebo 50.0%, $P = 0.043$; Table 3). The most frequently prescribed homeopathic medicines were *Apis mellifica*, *Arsenicum album*, *Baptisia*, *Bryonia*, *Carbo vegetabilis*, *Crotalus horridus*, *Lachesis muta*, *Lycopodium clavatum*, *Phosphorus*, and *Pyrogenium* (Table 4).

Table 1 Baseline demographic characteristics

	Homeopathy $n = 33$	*Placebo* $n = 34$	P
Age	55.1 ± 19.6	58.2 ± 14.0	ns
Age			ns
≤ 60	15 (45.5%)	17 (50.0%)	
61–75	15 (45.5%)	14 (41.2%)	
> 75	3 (9.1%)	3 (8.8%)	
Sex m:f	23:10	21:13	ns
Weight (kg)	79.3 ± 11.9	76.9 ± 11.1	ns
Height (cm)	174.7 ± 8.9	172.0 ± 10.0	ns
BMI	26.2 ± 4.7	26.4 ± 5.5	ns
Prior conditions			ns
Cancer	12 (36.4%)	13 (38.2%)	
Cardiovascular disease	5 (15.2%)	4 (11.8%)	
Recent trauma	5 (15.2%)	3 (8.8%)	
Infectious disease	3 (9.0%)	3 (8.8%)	
Intoxication	2 (6.1%)	4 (11.8%)	
Renal disease	3 (9.0%)	2 (5.9%)	
Liver disease	1 (3.0%)	2 (5.9%)	
Pneumonia	2 (6.1%)	3 (8.8%)	
Reason for admission			ns
Respiratory insufficiency	12	10	
Sepsis	19	21	
Other	2	3	

Discussion

Our data suggest that adjunctive homeopathic treatment may be beneficial for the survival of critically ill patients. Short-time survival showed a non-statistically significant trend in favour of homeopathy; however, this may be due to the relatively small sample size. The lack of adverse effects is an important advantage of homeopathic treatment. As a further advantage, there is no interference with traditional treatment. Dosing via the oral route is easy and

Table 2 Baseline clinical indices

	Homeopathy $n = 33$	*Placebo* $n = 34$	P*
APACHE II score	24.7 ± 3.2	24.0 ± 4.4	ns
APACHE II score ≥ 25	18 (54.5%)	16 (47.1%)	ns
Temperature at entry (°C)	37.9 ± 1.34	37.8 ± 1.1	ns
Respiratory rate at entry (min)	21.6 ± 4.6	19.7 ± 5.3	ns
Heart rate at entry (min)	102.7 ± 23.5	112.9 ± 22.2	ns
Leukocytes at entry G/L	13.7 ± 9.4	14.4 ± 10.0	ns
Temperature ≤ 36 or ≥ 38 °C	22 (66.6%)	19 (55.9%)	ns
Respiratory rate ≥ 20 (min)	26 (81.3%)	22 (64.7%)	ns
Heart rate ≥ 90 (min)	22 (66.7%)	30 (90.9%)	0.033
Leukocytes ≤ 4 ≥ 12 G/L	21 (63.6%)	29 (85.3%)	ns
Number of organ failures			ns
2	2 (6.1%)	5 (14.7%)	
3	16 (48.5%)	14 (41.2%)	
4	12 (36.4%)	13 (38.2%)	
5	3 (9.0%)	2 (5.9%)	
Mechanical ventilation	29 (87.9%)	30 (90.9%)	ns
FiO_2%	58.6 ± 19.2	65.0 ± 20.9	ns
Vasopressors	26 (78.8%)	30 (88.2%)	ns
Veno-venous hemofiltration	14 (42.4%)	12 (35.3%)	ns
Central venous pressure mmHg	8.7 ± 3.8	9.7 ± 4.7	ns
Blood cultures positive			
Gram negative	7 (21.2%)	4 (11.8%)	ns
Gram positive	4 (12.1%)	6 (17.6%)	ns
Fungi	3 (9.1%)	3 (8.8%)	ns
Mean blood pressure (mmHg)	80.6 ± 16.6	78.2 ± 20.9	ns
Platelet count	158.1 ± 108.0	172.7 ± 136.6	ns
Blood sugar (mmol/l)	8.9 ± 4.3	7.8 ± 2.8	ns
Serum creatinine (μmol/l)	194.5 ± 185.7	185.7 ± 176.8	ns
Blood urea nitrogen (mmol/l)	5.9 ± 4.5	6.0 ± 4.1	ns
Total protein (g/l)	57 ± 8	60 ± 13	ns
Bilirubine (μmol/l)	0.9 ± 0.8	1.1 ± 1.1	ns
Potassium (mmol/l)	4.1 ± 0.7	4.1 ± 0.8	ns
Sodium (mmol/l)	141.9 ± 6.2	142.4 ± 8.7	ns

*Kruskal–Wallis.

possible also in intubated patients orally and patients with oral or nasal feeding tubes. Furthermore, homeopathic medicines are low cost. One constraint is the small number of trained homeopathic doctors available in this setting.

Confounding factors include that placebo patients were more seriously affected in terms of heart rate and leukocyte count. However, there was no significant difference in the means of these variables. All patients received antibiotic therapy.

The mortality of severe sepsis, defined as sepsis with at least one organ failure, and septic shock, defined as hypotension not reversible by fluid resuscitation and associated with organ dysfunction or hypoperfusion abnormalities, remains very high despite increased efforts in intensive care medicine.[11,12]

Guidelines have been developed in an endeavour to improve outcome.[1] Resuscitation of a patient in severe sepsis or sepsis-induced tissue hypoperfusion should begin as soon as the syndrome is recognized and should not be delayed pending ICU admission. During the first 6 h, the goals should include all of the following: central venous pressure 8–12 mmHg; mean arterial pressure >65 mmHg; urine output >0.5 ml/kg/h; and central venous or mixed venous oxygen saturation >70%. Early therapy directed towards these goals improves survival.[13]

Appropriate cultures should always be obtained before antimicrobial therapy is initiated[14] and tests should be done as soon as possible to determine the source of the infection and the causative organism. Imaging studies such as ultrasound and/or bedside computer tomography should be performed. Sources of infection requiring drainage should be identified promptly. Intravenous antibiotic therapy should be

Table 3 Survival

	Homeopathy $n = 33$	*Placebo* $n = 34$	P*
Survival 30 days	27 (81.8%)	23 (67.7%)	0.19
Survival 180 days	25 (75.8%)	17 (50.0%)	0.043

*Kruskal–Wallis.

Table 4 Most often used homeopathic medicines and indications

	Homeopathy number of prescriptions	*Placebo number of prescriptions*	P
Apis mellifica	4	3	ns
Oedema			
Extreme dyspnoea			
Arsenicum album	6	8	ns
Weakness, exhaustion			
Cardiovascular compromise			
Anxiety, restlessness			
Cachectic appearance			
Baptisia	5	7	ns
ARDS			
Sepsis			
Hot skin			
Belladonna	6	7	ns
High temperature with sweat			
Red discolouration, face			
Bryonia	4	3	ns
Pneumonia, esp. right lung			
Stitching pain in chest			
Carbo vegetabilis	6	7	ns
Respiratory insufficiency			
ARDS			
Crotalus horridus	7	8	ns
Purpura haemorrhagica			
Haemorrhages			
Lachesis muta	15	20	ns
Septic shock			
Haemorrhage			
High temperature			
Embolism			
Discolouration blue, purple			
Lycopodium clavatum	2	4	ns
Fever, afternoon			
Distension, abdominal			
Phosphorus	12	14	ns
Pneumonia, esp. right lower lobe			
Haemorrhage			
Purpura haemorrhagica			
Pyrogenium	5	6	ns
Septic fever			
Offensive odour			

started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained.

Establishing vascular access and initiating aggressive fluid resuscitation is the first priority when managing patients with severe sepsis or septic shock. The antimicrobial regimen should always be reassessed after 48–72 h on the basis of microbiological and clinical data with the aim of using a narrow-spectrum antibiotic to prevent the development of resistance, to reduce toxicity, and to reduce costs. Fluid challenge in patients with suspected hypovolemia (suspected inadequate arterial circulation) may be given over 30 min and repeated based on response (increase in blood pressure and urine output) and tolerance (evidence of intravascular volume overload). If appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion, administration with vasopressor agents should be started.

Intravenous corticosteroids are recommended in patients with septic shock who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure.[15–17] Recombinant activated protein C (rhAPC) is recommended in patients at high risk of death (APACHE II >25, sepsis-induced multiple organ failure, septic shock, or sepsis-induced ARDS) and no absolute contraindication that outweighs the potential benefit of rhAPC. The inflammatory response in sepsis is pro-coagulant in the early stages. rhAPC, an endogenous anti-coagulant with anti-inflammatory properties, has been shown, to improve survival in patients with sepsis-induced organ dysfunction.[18]

Mechanical ventilation in sepsis-induced acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) should be adjusted to a "low" tidal in conjunction with the goal of maintaining end-inspiratory plateau pressures less than 30 cmH_2O.[19–22] Daily spontaneous breathing trials reduce the duration of mechanical ventilation.[23–25] Mechanically ventilated patients receiving continuous sedation may have a significantly longer duration of mechanical ventilation, ICU and hospital length of stay.[26] Daily interruption or lightening of sedation may reduce the duration of mechanical ventilation and ICU stay.[27] Following initial stabilization, blood glucose should be kept below 8.3 mmol/l using continuous infusion insulin if necessary.[28]

Conclusion

Our data suggest that homeopathic treatment has a beneficial effect on the long-term survival of patients with severe sepsis, further research is required before making firm recommendations. The lack of trained homeopaths available to advise on treatment on ICUs is an important constraint to further research and implementation.

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