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Somatostatin *v* placebo in bleeding oesophageal varices: randomised trial and meta-analysis

Peter C Gøtzsche, Ida Gjørup, Helen Bonnén, Niels Erik Bille Brahe, Ulrik Becker, Flemming Burcharth

Department of Medical Gastroenterology, Hvidovre Hospital, Denmark
Peter C Gøtzsche, *registrar*
Helen Bonnén, *registrar*
Ulrik Becker, *senior registrar*

Department of Surgical Gastroenterology, Herlev Hospital, Denmark
Ida Gjørup, *registrar*
Niels Erik Bille Brahe, *senior registrar*
Flemming Burcharth, *chief physician*

Correspondence to:
Dr Gøtzsche, Director of Nordic Cochrane Centre, Research and Development Secretariat, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark.

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Abstract

***Objective*—To study whether somatostatin or its derivative octreotide is more effective than placebo for treating bleeding oesophageal varices.**

***Methods*—Randomised, double blind trial and meta-analysis with blinded analysis of data and writing of manuscripts.**

***Setting*—Departments of medical and surgical gastroenterology in Copenhagen.**

***Subjects*—Patients suspected of bleeding from oesophageal varices and of having cirrhosis of the liver.**

***Main outcome measures*—Survival, number of blood transfusions, and use of Sengstaken-Blakemore tube.**

***Results*—86 patients were randomised; in each group 16 died within six weeks (95% confidence interval for difference in mortality —19% to 22%). There were no differences between those treated with somatostatin or placebo in median number of blood transfusions (8 *v* 5, P=0·07, 0 to 4 transfusions) or in numbers of patients who needed balloon tamponade (16 *v* 13, P=0·54, −11% to 28%). In a meta-analysis of three trials involving 290 patients somatostatin had no effect on survival compared with placebo (P=0·59, odds ratio 1·16; 0·67 to 2·01). For blood transfusions and use of balloon tamponade there was heterogeneity between the trials with no convincing evidence in favour of somatostatin. No placebo controlled trials have been performed with octreotide.**

***Conclusion*—Within the limited power of this study and meta-analysis we were unable to show a clinical benefit of somatostatin in the emergency treatment of bleeding oesophageal varices.**

Introduction

Somatostatin is a ubiquitous tetradecapeptide hormone. In most experimental studies, both in animals and in humans, it has reduced portal blood flow,[1 2] while the effect on intraoesophageal pressure has been more equivocal.[2 4] Somatostatin and its derivative octreotide are often used for emergency treatment of bleeding oesophageal varices in patients with cirrhosis of the liver.[5-7] Two placebo controlled trials, however, have shown contrasting results.[8 9] We report here a third trial and a meta-analysis of the trials.

PATIENT SELECTION

The patients were enrolled from April 1987 to the end of April 1992. Patients with clinical indication of bleeding oesophageal varices and with verified or suspected cirrhosis of the liver were eligible for the study. Children and pregnant or lactating women were excluded. Informed consent was obtained unless the

patient's condition was so poor that it was not possible. The study was approved by the regional ethics committees and by the National Board of Health.

TREATMENT PROTOCOL

Vials containing either 3 mg somatostatin or placebo of identical appearance were delivered by DuraScan Medical Products. The contents of two vials were dissolved in 1 litre of isotonic glucose and infused at a rate of 42 ml/h, corresponding to 250 μg/h of somatostatin. Treatment was given for 24 hours for each episode of bleeding. Bleeding after at least 6 hours with clear aspirate from the nasogastric tube was regarded as a new episode.

Randomisation in blocks of 10 patients was made by DuraScan according to a table of random numbers. Sealed envelopes were available at the departments; they were not opened on any occasion. The patients were allocated as quickly as possible after the start of bleeding to somatostatin or placebo by using the medicine package with the lowest available number.

The trial was pragmatic as all other treatment followed the usual routines. Ancillary treatments were similar at the participating departments except that antiulcer drugs were more commonly used at the medical than at the surgical department. We originally planned to exclude patients in whom endoscopy after inclusion in the study did not support varices as the cause of bleeding or in whom later investigations could not verify cirrhosis of the liver. However, as such decisions could bias the trial we decided before data analysis began to keep all randomised patients in the analysis.

At entry we noted duration of bleeding; number of transfusions before randomisation; presence of encephalopathy and ascites; plasma concentrations of bilirubin, aspartate amino transferase, alkaline phosphatase, albumin, and prothrombin; and presence of diabetes.

Outcome measures after six weeks were survival, blood transfusions, episodes of bleeding, days with bleeding, use of the Sengstaken-Blakemore tube, and complications. Only observed or spontaneously reported adverse reactions were noted.

TABLE I—*Median (interquartile range) baseline characteristics. Approximate normal ranges for biochemical variables in brackets*

Variable	Somatostatin (n=42)	Placebo (n=44)
Age (years)	57 (49-67)	51 (42-64)
No of men	26	35
Bleeding duration (days)	4 (2·8-13·5)	5 (2·0-12·0)
No of transfusions	0 (0-3)	2 (0-3)
Bilirubin (4-22 μmol/l)	42 (23-80)	39 (22-75)
Aspartate aminotransferase (0·17-0·67 μkat/l)	0·85 (0·57-1·82)	1·13 (0·62-2·38)
Alkaline phosphatase 0·5-2·0 μkat/l)	4·52 (2·28-5·82)	4·52 (3·23-7·57)
Albumin (41-57 g/l)	29 (23-34)	30 (25-34)
Prothrombin (0·70-1·30)	0·43 (0·32-0·54)	0·44 (0·33-0·56)
Creatinine (40-130 μmol/l)	88 (76-113)	94 (77-131)
Encephalopathy	7	10
Ascites	19	15
Diabetes	7	6
Endoscopy performed:	40	41
Large varices	23	24
Small varices	10	11
No varices	7	6
Visible blood	22	26
Oesophageal ulceration	5	8

TABLE II—*Outcome after six weeks. Figures are numbers of patients and medians (interquartile ranges)*

Detail	Somatostatin (n=42)	Placebo (n=44)	P value	95% Confidence interval for difference
Deaths	16	16	1·00	−19% to 22%
No of transfusions	8 (5-12)	5 (4-9)	0·07	0 to 4
Use of balloon tamponade	16	13	0·54	−11% to 28%
Two or more episodes of bleeding	14	7	0·10	−0·5% to 35%
No of days of bleeding	1 (1-2)	1 (1-2)	0·61	−1 to 1

STATISTICAL METHODS

We planned to include 100 patients, assuming arrest of bleeding in 40% with placebo, a minimally relevant difference of 30%, and type I and type II errors of 0·05 and 0·10, respectively. No interim analyses were made. Fisher's exact test was used for binary data and the Mann-Whitney test for other variables. Analysis of data and writing of manuscripts was blinded; the code was not broken before both versions of the manuscript had been agreed on by all authors. We calculated 95% confidence intervals for main outcome variables.

META-ANALYSIS

The primary aim of the meta-analysis was to study whether somatostatin or its derivative octreotide improve survival. Secondary variables were number of blood transfusions and number of patients needing balloon tamponade.

All randomised trials comparing one of the drugs with placebo or no treatment in patients suspected of bleeding from oesophageal varices were eligible. An online Medline search from 1966 onwards was done in January 1995. The term "explode somatostatin/all subheadings" or the text words somatostatin or octreotide were combined with any of the following: variceal, varices, bleed#, haemorrhage, hemorrhage, oesophag#, esophag#, haematemesis, hematemesis, melaena, melena.

Furthermore, the company marketing octreotide was contacted, reference lists of relevant articles, reviews, and editorials were scanned, and authors of trials were asked whether they knew of additional studies, including unpublished ones.

Details on numbers of randomised patients, deaths, randomisation and blinding procedures, numbers of drop outs, and exclusions after randomisation were extracted. Additional information was sought by writing to the authors. The outcomes were weighted by the inverse variance[10 11]; for blood transfusions we used medians when available.

Results

PRESENT TRIAL

Because of slow recruitment and as somatostatin was no longer commercially available the trial was stopped after five years, when 86 of the planned 100 patients had been entered. The two treatment groups were comparable at baseline (table I). Alcoholic liver disease was suspected or verified in almost all patients; in only six were other diagnoses definitely established. One patient on somatostatin suffered from Budd-Chiari's syndrome because of polycythaemia, another (who died during the study) from haemangioendothelioma. Two patients on placebo had oesophageal ulcers, one had cirrhosis because of reactive hepatitis, and one had liver metastases from a rectal carcinoma (died during study).

Endoscopy was performed within 24 hours after randomisation in 44 of the patients but could not always be performed during active bleeding. Thus, not all patients had visible blood, and in 13 of the 81 patients who ultimately underwent endoscopy varices were not seen. Sclerotherapy was used in 29 patients treated with somatostatin and in 31 patients treated with placebo. Antiulcer drugs were used in 10 patients on somatostatin and in 12 on placebo; tranexamic acid was used in two *v* one. Operations were performed in two *v* one; finally, vasopressin and propranolol were used in one patient each on placebo.

Sixteen patients died in each group (P=1·00). The number of days of bleeding and numbers of patients who needed balloon tamponade were also similar (table II). More patients in the somatostatin group had more than one episode of bleeding (P=0·10), and

TABLE III—*Meta-analysis of odds of dying with somatostatin (P=0·59)* (χ^2 for heterogeneity=0·06, P=0·97)

Study	Somatostatin		Placebo		Odds ratio (95% confidence interval)
	No of deaths	No of patients	No of deaths	No of patients	
Valenzuela *et al*[8]	15	48	10	36	1·18 (0·46 to 3·02)
Burroughs *et al*[9]	9	61	7	59	1·28 (0·45 to 3·66)
Current study	16	42	16	44	1·08 (0·45 to 2·57)
Total					1·16 (0·67 to 2·01)

they needed more blood transfusions, eight *v* five (P=0·07).

In the somatostatin group, the oesophagus ruptured in two patients in whom balloon tamponade was used; one of them died. A third patient developed stenosis after sclerotherapy. No adverse effects were reported with placebo.

META-ANALYSIS

We identified only two trials in addition to our own with somatostatin and none with octreotide. In the trial by Valenzuela *et al* 18 of 102 randomised patients were excluded for various reasons.[8] In the trial by Burroughs *et al* 13 of 133 randomised patients were excluded because the source of bleeding was judged to be non-variceal.[9] Randomisation more than once was allowed; thus the remaining 120 admissions referred to only 92 patients. We would have preferred to include all randomised patients in the meta-analysis and to exclude any doubles. The authors were not, however, able to give us information on these patients.

The meta-analysis comprised 290 patients. Somatostatin had no effect on survival (table III); a total of 40 patients died in the somatostatin groups *v* 33 patients in the placebo groups (P=0·59; odds ratio 1·16; 95% confidence interval 0·67 to 2·01). There was no heterogeneity between the trials (P=0·97).

There was considerable heterogeneity for average number of blood transfusions (P=0·02). In the trial by Valenzuela *et al* patients on somatostatin received on average 1·1 litres of blood products while patients on placebo received 1·4 litres. This difference corresponds to one unit of blood (variance of the difference= 3·46). In the trial by Burroughs *et al* the median number of units of blood or plasma transfused was 3 units with somatostatin and 6 units with placebo (variance=1·07). We found the reverse: 6 units of blood transfused with somatostatin and 3 units with placebo (variance=3·85). It would be problematic to take this heterogeneity into account by doing a random effects analysis as the variation between studies would be determined with great uncertainty, based on only three trials.[11] If the heterogeneity is ignored patients in the somatostatin groups received on average 1·6 transfusions fewer than in the placebo groups (P=0·06; −3·2 to +0·1). (In a random effects analysis the confidence interval would have been wider). As the variance in the trial by Burroughs *et al*[9] was surprisingly small, however, being only one third of the roughly identical variance in the other two trials, weighting by inverse variance seems to be unjustified. If this is accepted, then a simple, unweighted average of only a third of a unit of blood products is the best estimate of the effect of somatostatin over placebo.

Valenzuela *et al* did not report data on the use of balloon tamponade.[8] There was heterogeneity for the other two trials with opposite trends (P=0·05). Balloon tamponade was used in seven patients on somatostatin and in 15 patients on placebo in the trial by Burroughs *et al*[9] and in 16 *v* 13 patients in our trial.

Key messages

- Somatostatin and its derivative octreotide are often recommended for treatment of bleeding oesophageal varices
- This study failed to show a benefit of somatostatin
- Meta-analysis of the placebo controlled studies also failed to show a benefit
- Treatment with somatostatin or octreotide cannot be recommended at present
- Larger studies are needed to give a definitive answer

Discussion

In review articles various treatments may be recommended for emergency treatment of bleeding oesophageal varices with claims of bleeding control in 90-95% of cases.[5,6] Such claims are misleading, however, as the bleeding often stops spontaneously—for example, in 83% of the patients treated with placebo in the trial by Valenzuela *et al*.[8] Clinicians may therefore get the impression that their preferred intervention is effective, whatever its nature. Obviously, a rigorous, randomised trial with a placebo or a control group without treatment is the only acceptable design for judging the effect of any remedy in bleeding oesophageal varices.

We were unable to show any benefit from treatment with somatostatin. Our study and meta-analysis had limited power, however, and further studies, giving larger numbers available for meta-analysis, are needed to give a more definitive answer.

Our results apply to the particular dose and duration of treatment we used. We doubt, however, that the differences in results between the three studies can be explained by differences in dose and duration. In the first trial of somatostatin the drug was dissolved in saline and administered in a plastic infusion system, which led to an estimated loss of up to 50% of the activity. If the effect was poor, however, the dose was doubled.[8] In the other two trials, the drug was dissolved in isotonic glucose. The infusion rate was 250 μg/h in all three studies. We did not use an initial bolus as the half life of somatostatin is only 1-5 minutes[12]; steady state is therefore reached quickly. The study by Valenzuela *et al* has been criticised for its short duration of treatment (30 hours)[8] whereas the study by Burroughs *et al* was extended to five days.[9] As most patients stop bleeding within the first day, however, this criticism is probably irrelevant.

The study by Valenzuela *et al* has also been criticised for the high rate of control of bleeding in the placebo group, 83% *v* 65% in the somatostatin group,[8] but this difference can be explained simply by random variation (P=0·09).

We preferred the *intention to treat* approach as differential effects of the drugs could lead to biased decisions on secondary exclusions of patients. This approach has the additional advantage in that it mirrors what happens in practice.

Within the limited power of this study and meta-analysis we were unable to show a clinical benefit of somatostatin in the emergency treatment of bleeding oesophageal varices. Further studies are needed to give a more definitive answer.

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The analgesic effect of sucrose in full term infants: a randomised controlled trial

Nora Haouari, Christopher Wood, Gillian Griffiths, Malcolm Levene

Abstract

***Objective*—To evaluate the effects of different sucrose concentrations on measures of neonatal pain.**

***Design*—Randomised, double blind, placebo controlled trial of sterile water (control) or one of three solutions of sucrose—namely, 12·5%, 25%, and 50% wt/vol.**

***Setting*—Postnatal ward.**

***Patients*—60 healthy infants of gestational age 37-42 weeks and postnatal age 1-6 days randomised to receive 2 ml of one of the four solutions on to the tongue two minutes before heel prick sampling for serum bilirubin concentrations.**

***Main outcome measure*—Duration of crying over the first three minutes after heel prick.**

***Results*—There was a significant reduction in overall crying time and heart rate after three minutes in the babies given 50% sucrose as compared with controls. This was maximal one minute after heel prick in the 50% sucrose group and became statistically significant in the 25% sucrose group at two minutes. There was a significant trend for a reduction in crying time with increasing concentrations of sucrose over the first three minutes.**

***Conclusion*—Concentrated sucrose solution seems to reduce crying and the autonomic effects of a painful procedure in healthy normal babies. Sucrose may be a useful and safe analgesic for minor procedures in neonates.**

Introduction

The ability of neonates to perceive and react to pain has been much debated in recent years. We know that most of the anatomical pathways and neurotransmitter function necessary for pain perception are fully or nearly fully developed in the neonatal period.[1,2] Yet many people are still reluctant to believe that pain felt by neonates may be as severe as that felt by older children or adults.

All neonates born in developed countries are subjected to painful procedures. Heel pricks for Guthrie tests are near universal and intramuscular vitamin K injections and routine circumcision are still common in some countries. Blood samples for serum bilirubin and blood sugar estimations are taken when clinically indicated, and if a neonate is sick frequent blood sampling, venepuncture, and more severe procedures which cause tissue injury are common. We estimate that in our hospital every baby has at least one heel prick procedure, 15% of babies have two to five blood samples taken or intramuscular injections, and 2% have five or more such procedures.

We assessed the use of sucrose to reduce pain in neonates subjected to routine blood sampling by heel prick.

Patients and methods

Healthy full term infants who required heel prick sampling for serum bilirubin estimations were recruited from the postnatal wards of this hospital over six months. Babies with Apgar scores of less than 7 at one minute or who had received naloxone were excluded. All heel prick samples were drawn by a single, experienced nurse (GG) using a sterile lance. The babies responses were observed by NH and CW.

Infants were taken to a warm, quiet nursery for blood sampling and were fully clothed apart from the foot used for sampling. Before skin preparation a pulse oximeter was applied to the baby's hand to measure changes in oxygen saturation and heart rate during the study. Parents could be present if they wished but did not speak to or touch the baby during the procedure. We calculated that to achieve 80% power to show a 50% reduction in crying time ($P=0·05$) 15 babies would be required in each group.

Babies were allocated at random to receive one of four solutions on to the tongue: sterile water (control) or 12·5%, 25%, or 50% sucrose (wt/vol). Randomisation was by means of pre-prepared solutions in coded bottles. Investigators were blind to the nature of the solutions throughout. Stratification was not used. The test solution (2 ml) was given by syringe into the baby's mouth over less than one minute. The heel was then exposed, cleaned with a sterile swab, and held gently. Two minutes after the test solution the heel was lanced and gently squeezed.

The baby's behavioural state[3] was recorded immediately before lancing. Four facial expressions reported to occur during an acute painful stimulus[4] were also recorded on a 0-4 scale. Crying during sampling and during the three minutes after sampling (recovery phase) was recorded on audio tape and later analysed blindly for the duration of crying. Crying time was defined as the number of seconds that the baby cried within the first three minutes and the duration of the first cry was the duration of continuous crying before a quiet interval of five seconds.

The study was approved by the hospital ethics committee and all parents gave informed consent. Analysis of non-parametric data was by the Mann-Whitney U test (Minitab) or a trend test.[5] Changes in

University Division of Paediatrics and Child Health, D Floor, Clarendon Wing, Leeds General Infirmary, Leeds LS2 9NS
Nora Haouari, *visiting clinical fellow*
Christopher Wood, *lecturer*
Gillian Griffiths, *research nurse*
Malcolm Levene, *professor of paediatrics*

Correspondence to:
Professor Levene.

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