Research letters

Survival rate after early treatment for acute type-A aortic dissection with ACTH-(1-24)

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Haemorrhagic shock, usually as a consequence of major trauma, is the most frequent cause of death among people younger than 40 years. Reports indicate that melanocortin peptides are effective in reversing haemorrhagic shock. We found that in patients with aortic-dissection-induced haemorrhagic shock, the addition of an early intravenous bolus injection of the melanocortin andrenocorticotrophic hormone (ACTH)-(1-24) to standard treatment significantly improved cardiovascular function and increased survival rate. Because administration of ACTH-(1-24) is simple, and because melanocortin peptides have no acute toxicity, their use in the early critical care of patients in shock should be more extensively assessed.

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Death resulting from haemorrhagic shock still represents one of the primary causes of mortality. Studies done in different centres show that the mortality rate in these patients has remained substantially unchanged over the past 5–10 years.[1] Despite the enormous increase in the understanding of shock pathophysiology and the new treatments arising from this understanding, results have been disappointing.

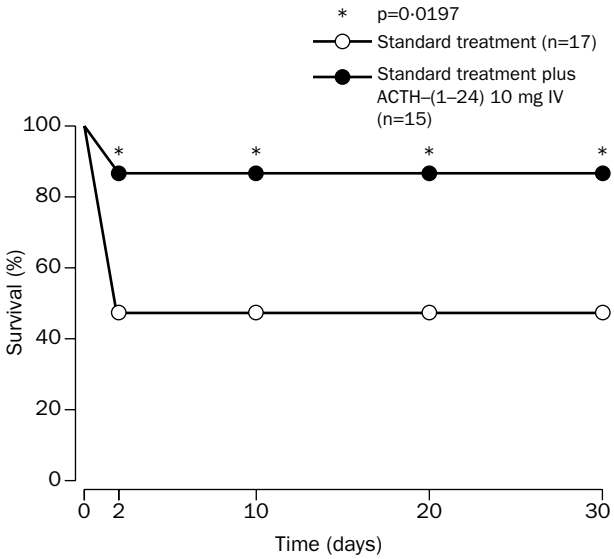
Several groups have reported that melanocortin peptides lacking the C-terminal Arg-Phe sequence—eg, adrenocorticotropic hormone (ACTH)-(4-10), α-melanocyte-stimulating hormone (MSH), ACTH-(1-17), and ACTH-(1-24)—greatly improve cardiovascular function and survival time in haemorrhagic-shock experiments, as well as in other animal models of shock.[2,3] The intravenous bolus injection of any of these peptides induces, within a few minutes, an adrenal-independent, dose-dependent restoration (minimum effective dose: 20 μg kg^{-1}; maximum effective dose: 160 μg kg^{-1}) of cardiac output, total peripheral resistance index, arterial pressure, pulse amplitude, and tissue blood flow, with gradual normalisation of arterial and venous pH and base excess, as well as of venous tension of O_2 and CO_2, and venous oxygen saturation and lactate concentrations. Moreover, there is a highly significant reduction in blood concentrations of free radicals, nitric oxide, and tumour necrosis factor (TNF)-α, which are all massively increased in shock conditions. The temporary reversal of haemorrhagic shock induced by these peptides is associated with a large increase in the volume of circulating blood, as the consequence of the mobilisation of the peripherally pooled residual blood, and involves the activation of melanocortin receptors in the brain. Similar results have been reported anecdotally for haemorrhagic and cardiogenic shock in human beings.[2,4]

Since melanocortin peptides have no acute toxicity in human beings[5] and do not interfere with the action of the drugs used in treatment of shock,[2] we wanted to verify their efficacy in a sizable number of cases of a homogeneous clinical condition of hypovolaemic shock. The study was approved by the local ethics committee (comitato etico interno per la sperimentazione clinica di Villa Maria Cecilia, Cotignola, Ravenna), and written consent was obtained from all patients, or from their closest relative. 32 patients, men and women, were enrolled in the study. All patients had type-A aortic dissection (separation of the wall of the ascending aorta into two sheets along its longitudinal axis in the medial layer, thus forming a false channel for the blood flow) complicated by aortic rupture and cardiac tamponade (European score >10), and with clinical signs of shock (systolic blood pressure <80 mm Hg; haemoglobin 40–60 g/L; haemocrit 10–18%). 17 patients were randomly assigned to the standard surgical approach to treatment (eg, volume restoration and inotropic drugs). 15 patients were randomly assigned to the same treatment plus an intravenous bolus injection of 10 mg ACTH-(1-24) at the moment of arrival into the casualty ward (20–40 min after the emergency call). At the moment of surgical intervention (3–5 h after onset of the symptoms) patients treated with ACTH-(1-24) had a mean stabilised

Characteristic	Standard treatment (n=17)	Standard treatment plus ACTH (1–24), 10 mg IV (n=15)
Mean age (SD; years)	68·29 (6·98)	69·87 (7·88)
Mean time from emergency call to treatment (SD; min)	29·11 (7·71)	31·09 (8·32)
Mean SBP at moment of surgical intervention (SD; mm Hg)	≤50	95 (9)
Range of plasma concentration of TNF-α on postoperative day (pg mL^{-1})	80–3860	<10

ACTH=adrenocorticotrophic hormone; IV=intravenous; SBP=systolic blood pressure; TNF-α=tumour necrosis factor α.

Clinical characteristics



Survival rate during 30 days after surgery in patients with acute type-A-aortic-dissection-induced haemorrhagic shock given standard treatment or standard treatment plus ACTH-(1–24)
IV=intravenous.

systolic blood pressure of 95 (SD 9) mm Hg, while in patients not treated with ACTH the mean systolic blood pressure was 50 mm Hg, or less (table). Plasma concentrations of TNF-α 2 days after surgery were undetectable in patients treated with ACTH (detection limit of the enzyme linked immunosorbent assay: 10 pg mL^{-1}), while they were in the range 80–3860 pg mL^{-1} in patients not treated with ACTH (table). Survival at the 30th day after surgery was 13 of 15 in ACTH group, and eight of 17 in the standard treatment group (p=0·0197, Fisher's test; figure).

Our data show that early intravenous treatment with ACTH-(1–24) is associated with significant improvement of the cardiovascular function and with increased survival rate in aortic-dissection-induced cardiac tamponade and hypovolaemic shock.

The ease of administration and lack of acute toxicity of ACTH-(1-24)—like all the other melanocortins lacking the C-terminal Arg-Phe sequence—means that our results should stimulate further studies on the use of ACTH-(1-24) along with standard treatment in the early critical care of patients in shock.

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1 Regel G, Grotz M, Weltner T, Sturm JA, Tscherne H. Pattern of organ failure following severe trauma. *World J Surg* 1996; **20:** 422–29.
2 Bertolini A. The opioid/anti-opioid balance in shock: a new target for therapy in resuscitation. *Resuscitation* 1995; **30:** 29–42.
3 Squadrito F, Guarini S, Altavilla D, et al. Adrenocorticotropin reverses vascular dysfunction and protects against splanchnic artery occlusion shock. *Br J Pharmacol* 1999; **128:** 816–22.
4 Noera G, Angiello L, Biagi B, Pensa P. Haemorrhagic shock in cardiac surgery. Pharmacological treatment with ACTH-(1-24). *Resuscitation* 1991; **22:** 123–27.
5 Mandel W, Singer MJ, Gudmunson HR, Meister L, Modern FWS. Intravenous use of pituitary adrenocorticotropin hormone (ACTH). A report of its administration in the twenty-five patients. *J Am Med Assoc* 1951; **146:** 546–51.

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Characteristics	Patients
Maternal	
Median (range) age (years)	21 (15–29)
Parity	
0	14 (64%)
1	5 (23%)
>1	3 (13%)
Median (range) body mass index (kg/m²)	25·8 (13·0–50·2)
Median (range) gestational age (weeks)	39·3 (37·6–41·1)
Fetal	
Median (range) fetal weight (g)	3257 (2670–3800)
Median (range) head circumference (cm)	33·8 (32·0–36·5)
Labour	
Median (range) duration of second stage (min)	73 (26–169)
Oxytocin augmentation	16/22 (73%)
Operative (vacuum) deliveries	4/22 (18%)

Maternal, fetal, and labour characteristics

Use of McRoberts' position during delivery and increase in pushing efficiency

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McRoberts' position is used during the second stage of labour to facilitate delivery of the fetal shoulders. Few clinical studies have been done to measure its efficacy. We measured intrauterine pressure in 22 women in term labour, after the vertex reached 3+ station, in the dorsal lithotomy position. Patients pushed with legs either in stirrups or hyperflexed by 135° (McRoberts' position). Maternal valsalva transiently increased the expulsive force by 32% over naturally occurring contractions. Use of McRoberts' position almost doubled the intrauterine pressure developed by contractions alone (from 1653 mm Hg s to 3262 mm Hg s [97%]).

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Despite much research, there is no satisfactory clinical method that predicts shoulder dystocia.[1] Impacted fetal shoulders, causing distal cessation of oxygenated blood flow, can result in perinatal complications. Time is critical, and damage to the newborn is not rare.[2]

McRoberts' manoeuvre consists of sharp flexion of patients' hips against the abdomen, and is effective in 40–80% of patients when used as either the primary or the sole position. It is used as the first step towards an emergent vaginal delivery after diagnosis of impacted fetal shoulders. Traditionally, the manoeuvre was thought to free an impacted fetal shoulder by alteration of mechanical interactions through cephalad rotation of the mother's pubic symphysis and straightening of the lumbar vertebrae.[3] We tested whether McRoberts' manoeuvre increased intrauterine pressure, which could be another mechanism to release impacted fetal shoulders.

22 women in active labour gave informed consent and ethics approval was obtained. Exclusion criteria included: preterm labour, non-vertex presentation, multifetal pregnancy, fetal macrosomia, grand multiparity (six or more previous pregnancies), placental abnormalities, uterine structural anomalies or scars, and fetal heart rate abnormalities. All women in labour had epidural analgesia and were alert and responsive. We started taking measurements of intrauterine pressure once the vertex of the fetal head reached 3+ station. Intrauterine pressure was measured with a sensor-tip catheter connected to a recording system (CB Sciences, Dover, NH, USA). We recorded contractions for 15 min before any intervention to provide a baseline. Thus, each patient was her own control. Maternal pushing (valsalva) was accomplished by encouraging the patient to bear down with maximum effort with legs in either stirrups flexed 90° or hyperflexed 135° onto the abdomen. Patients pushed three times (each occasion for about 10 s) during a spontaneous contraction. In ten women, valsalva was done between contractions with and without the McRoberts' manoeuvre. Each data point was the average of three to five contractions. Strict dorsal lithotomy position was maintained only for the recordings (average 20 min). There were no fetal heart rate abnormalities or maternal hypotensive episodes. Area under the contraction curve (integral intrauterine pressure [mm Hg s]), maximum amplitude (mm Hg) and duration (s) were compared with paired *t* tests or one-way ANOVA, with Student-Newman-Keuls test as appropriate.

Area of the pelvic inlet was estimated with the formula: inlet area (m^2)=(fetal head circumference [cm])$^2 \times 10^{-4} \div 4\pi$. Additional forces were calculated by: force valsalva (N)=(101·3 kPa÷760 mm Hg)×(amplitude