Institutional review - Congenital

Comparison of sodium nitroprusside versus esmolol for the treatment of hypertension following repair of coarctation of the aorta

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Received 22 October 2002; received in revised form 01 December 2002; accepted 03 December 2002

Abstract

Postoperative arterial hypertension was treated with nitroprusside or esmolol in a prospective randomized study. If treatment failed, patients were first switched over to the other study drug, and then to a combination of both. Renin, angiotensin II, epinephrine, and norepinephrine were measured before, 1, and 17 h after operation. esmolol was effective in all cases of treatment (n = 6) whereas nitroprusside was ineffective in two out of seven patients (not significant), who were finally treated effectively with the combination of the study drugs. Whenever monotherapy failed, both drugs together were effective in reducing the postoperative activation of the sympathetic and renin-angiotensin systems. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Coarctation; Esmolol; Nitroprusside; Renin; Catecholamine

1. Introduction

Early postoperative hypertension is a frequent complication occurring in 56–100% of cases of surgical coarctation repair [1]. The cause of postoperative hypertension is multifactorial. Altered baroreceptor reflex, the activation of the sympathetic and the renin-angiotensin systems, and expansion of extracellular volume have all been evoked [1–3]. As hypertension puts strain on the surgical anastomosis and on the heart, prompt treatment is mandatory. Traditionally fast and short acting vasodilators like sodium nitroprusside have been used to treat the hypertension. Recently, an intravenous short-acting beta-receptor blocker named esmolol has become available which inhibits the effects of the sympathetic system’s activation and protects the heart. Thus, esmolol offers theoretical advantages over a pure vasodilator [4]. In this study we compared the effect of postoperative hypertension treatment by esmolol versus sodium nitroprusside on sympathetic and renin–angiotensin systems activation in patients with surgically repaired coarctation of the aorta.

2. Material and methods

The study was approved by the Ethics Committee of the Humboldt University, Berlin and was conducted at the Deutsches Herzzentrum, Berlin. Of 21 consecutive pediatric and adult patients admitted for surgical coarctation repair 15 patients (median age 14 years, range 4 days to 57 years) consented to take part in the study. Native coarctation was present in eight and a recoarctation after previous surgical repair in seven. Exclusion criteria included emergency operation of critical neonatal coarctation, lung disease such as asthma, congestive heart failure, diabetes, anemia, sinoatrial or atrioventricular block, psoriasis, and renal or liver dysfunction. Informed consent was obtained from patients or their legal guardians. Patients were randomized for the sodium nitroprusside (Nipruss, Schwarz-Pharma, Monheim, Germany) or esmolol (Brevibloc, Baxter, Unterschleißheim, Germany) treatment regime in case of postoperative hypertension prior to coarctation repair. Postoperative analgesia was achieved by piritramid (Dipidolor, Janssen-Cilag, Neuss, Germany) and all patients were weaned from mechanical ventilation postoperatively within the first 6 h.

Arterial blood pressure was monitored invasively using a canula in the radial artery. If systolic or diastolic blood pressure was above the 95% percentile according to patient age and height [5] within the first
24 h following surgery, treatment for hypertension was begun. According to the randomization protocol, patients received either sodium nitroprusside (0.5 μg/kg per min, increased every 2 min by 0.5 μg/kg per min to maximal 10 μg/kg per min) or esmolol (bolus 50 μg/kg repeated six times at 2-min intervals followed by an infusion of 250 μg/kg per min increased every 4 min at 50 μg/kg per min to maximal 500 μg/kg per min). Titration endpoints were an effective reduction in blood pressure (less than 95% percentile for height and age), attainment of the maximum drug dosage, significant bradycardia (< 80 bpm or < 50 bpm for patients younger and older than 1 year, respectively), significant tachycardia associated with hypotension, reduced contractile function (fractional shortening < 25% in transthoracic echocardiography) or other known drug side effects (wheezing, hyperglycemia, allergic reaction). In cases of treatment failure or side effects, patients were switched to treatment with the other drug. In cases of persistent hypertension we used a combination of both drugs. Serum epinephrine and norepinephrine were measured using the HPLC method (Chromosystems, Munich, Germany), active serum renin with an immunoradiometric assay (Nichols, Martens-Wijchen, Netherlands) and serum angiotensin II with an immunoassay kit (Nichols, Martens-Wijchen). Measurements were performed before, within 1 and 17 h following coarctation repair. The corresponding hemodynamic status of patients was recorded by the monitoring system (Siemens, Munich, Germany) and echocardiographic data were documented in all patients.

Statistical analysis was performed using a Mann–Whitney U-test for unpaired samples, a Fisher exact test for comparison of numerical variables between groups, and a Friedman test for intragroup comparison. P-values of less than 0.05 were considered to be statistically significant. Results in the figures are expressed as mean values and SEM. Postoperative blood pressure, renin, angiotensin, norepinephrine and epinephrine were compared between patients without hypertension, or those treated with esmolol, sodium nitroprusside, a combination of both drugs, respectively. Additionally, we compared the epinephrine values in patients after surgical repair with those of patients who had undergone balloon angioplasty using the same study protocol. In each group, each variable was evaluated for possible differences between measurements at the various time points.

3. Results

Thirteen out of 15 patients developed postoperative hypertension. Postoperative arterial hypertension did not occur in two out of three newborns of the study group. Those two newborns had low blood pressure without treatment (tizzy triangles, Fig. 1), low adrenaline (< 1 pg ml⁻¹), and low noradrenaline (265 pg ml⁻¹) serum values (tizzy triangles, Fig. 2). Analysis of the whole study group showed significantly elevated epinephrine values 17 h postoperatively compared to the initial measurements (Fig. 2). The same was true in the esmolol group, while statistical significance was not found in the nitroprusside group. Norepinephrine values differ widely with no statistical significance evident in our study groups. There were no statistically significant differences in the inter-group comparison (Table 1). Renin and angiotensin II levels were not affected in the study group (Fig. 2). Following administration of antihypertensive therapy, 13 out of 15 patients showed a significant fall in systolic and diastolic blood pressure compared to the blood pressures before medical intervention (Fig. 1), with no evidence of tachycardia or bradycardia 17 h after surgery. Epinephrine levels in the 13 patients were significantly elevated compared to preoperative values (Fig. 2), and norepinephrine levels had risen but did not reach statistical significance. There was no peak in epinephrine levels in six patients who had undergone balloon angioplasty, and in whom only one out of six patients was treated orally with β-blocker for paradoxical hypertension (Fig. 3). After surgery, the renin and angiotensin II values did not show any statistical significance between patients without hypertension and those effectively treated with esmolol, sodium nitroprusside, or a combination of both drugs.

For the treatment of hypertension, esmolol was effective in all cases, whereas sodium nitroprusside was effective in five out of seven cases (P > 0.05). The two patients who did not respond to sodium nitroprusside were switched to esmolol monotherapy, which also failed to control the blood pressure. Those two patients aged 8 and 12 years, respectively, had recoarctation after previous surgical repair and arterial hypertension (RR 150/65 and 170/90 mmHg). Interestingly their left ventricles were enlarged (diastolic diameter 3.8 and 5.7 cm) showing regular ventricular function. They were repaired with aortic clamp (30 and 51 min, respectively). The postoperative adrenaline (360 and
460 pg ml\(^{-1}\)) and noradrenaline values (770 and 1120 pg ml\(^{-1}\)) were in the upper third of the group (compare Fig. 2).

Postoperative arterial hypertension in both patients was finally effectively treated with a combination of sodium nitroprusside and esmolol.

In all patients medical treatment for arterial hypertension started 2–4 h after the end of the operation. In the whole

### Table 1

<table>
<thead>
<tr>
<th>Comparison of patients treated with esmolol or sodium nitroprusside</th>
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<tbody>
<tr>
<td><strong>Esmolol</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>No. of patients treated:</td>
</tr>
<tr>
<td>Native CoA</td>
</tr>
<tr>
<td>Residual or recurrent CoA</td>
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<tr>
<td>No. with use of cardiopulmonary bypass</td>
</tr>
<tr>
<td>Aortic cross-clamp (min)</td>
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\(^a\) n.s., not significant.

\(^b\) Only those 13 patients with successfull mono-drug-therapy, the two cases of crossover or combination treatment not included.

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Fig. 2. Neurohumoral analyses. Epinephrine/norepinephrine: 17 h postoperative epinephrine values differ significantly from the initial measurements analyzed in the total number of patients and in the esmolol group, while statistical significance was not found in the nitroprusside group. Norepinephrine values differ widely, with no statistical significance in our study groups. There were no statistically significant differences in the inter-group comparison. The two infants without hypertonus and without treatment (tizzy triangles) had low catecholamine values. Renin/angiotensin II: Both the renin and the angiotensin II values tended to drop 17 h post-op, with most patients treated for normal blood values (see Fig. 1). Statistical analysis showed no significant differences.

Fig. 3. Comparison between surgery and balloon angioplasty. Patients showed elevated epinephrine values after surgery compared to after balloon angioplasty. Seventeen hours after the intervention the epinephrine values were comparable in patients after surgery (13 out of 15 patients treated) and after balloon valvuloplasty (one out of six patients treated).
study group, the mean amount of esmolol administered up to 17 h after coarctation repair was 150 μg/kg per min (range 62–227 μg/kg per min), and four out of seven patients needed a peak transitory infusion rate of 500 μg/kg per min. The mean amount of the nitroprusside used was 2.1 (range 0.6–5 μg/kg per min), and five out of seven patients needed a peak transitory infusion rate of 10 μg/kg per min. Comparison between patients on esmolol or nitroprusside therapy revealed no differences regarding postoperative heart rate, blood pressure control, catecholamines, and renin–angiotensin levels. Neither drug caused any detectable side effects.

4. Discussion

This study shows that both drugs, esmolol and sodium nitroprusside, used as single drugs or in combination, are effective to treat paradoxical hypertension following surgical coarctation repair. Our finding of elevated epinephrine levels after surgery (Figs. 2 and 3) indicated sympathetic nervous system activation [6,7], possibly based on altered baroreceptor function. The resulting catecholamine release and activation of the renin-angiotensin system, accompanied by direct cardiovascular effects and extracellular volume expansion, are important factors in the pathogenesis of postoperative hypertension [1–3,7]. In this study we found an incidence of 86% reactive hypertension following surgery, and reactive hypertension was only absent in newborns. Arterial hypertension in our patients was treated effectively with esmolol, sodium nitroprusside, or a combination of both drugs (Fig. 1). This might partly explain the lack of renin-angiotensin activation in our patients; described in the literature as appearing later in the postoperative course [1].

Sodium nitroprusside, a potent vasodilator with rapid onset of action, has for a long time been used in the treatment of postoperative hypertension [8]. Its use is associated with possible cyanide toxicity, and reactive tachycardia with subsequent activation of the renin-angiotensin system [9]. β-Receptor blockers inhibit sympathetic system activation, which may be advantageous following coarctation repair [7]. Esmolol is a short-acting cardio-selective β-receptor blocker with the advantages of short onset of action, and dose-related hemodynamic effects [4,10]. It has previously been used as a single agent [11,12] or in combination with sodium nitroprusside [8,13,14] in children and adults. In our study, arterial hypertension was controlled with moderate dosages of either sodium nitroprusside or esmolol alone, or with both; the efficacy of the combined treatment might be explained by the complementary effect of these drugs in the neurohumoral system: esmolol exhibits its antihypertensive action by reducing heart contractility, attenuating simultaneously the sympathetic system activation that accompanies the vasodilatory effect of sodium nitroprusside. Indeed most of the previous studies on paradoxical hypertension following coarctation repair used esmolol together with sodium nitroprusside. High doses of esmolol can be associated with impaired heart contractility and increased pulmonary wedge pressure, and systemic vascular resistance [10,11]. Having administered a transient maximum dose of 500 μg/kg per min at the end of operation and anesthesia, we noted no adverse effects of esmolol in heart contractility as determined echocardiographically. Although treatment with sodium nitroprusside is associated with increased plasma renin activity and increased heart rate compared with esmolol treatment [8,11], we found no difference between the two study drugs according to these variables in a state of well controlled blood pressure 17 h after surgery. While the non-activation of the renin-angiotensin system is in accordance with other studies examining treatment with esmolol [11], it is unclear what factors lead to non-activation in our patients treated with sodium nitroprusside. Possible explanations for this phenomenon in our patients group include: (a) the moderate cumulated dose of sodium nitroprusside; (b) the absence of a low salt diet and volume repletion as used in other studies may have masked high plasma renin activity [7].

Postoperative hypertension in our study was absent only in newborns with non-critical coarctation. Both patients showed a low epinephrine response to coarctation repair. In a study of 571 patients, Cohen and colleagues showed that late hypertension occurred in 7% of those operated on as infants (<1 year of age) as opposed to 33% who had undergone repair after the age of 14 years [15]. The reason for both the lower rate of early paradoxical hypertension and the lower rate of late hypertension after infant coarctation repair remains speculative. In our study, none of the pre- and postoperative items predict the extent of reactive hypertension or insufficient reaction of reactive hypertension to postoperative single-drug-therapy. However, those two patients in our study, who developed reactive hypertension refractory to single-drug-therapy, had preoperative arterial hypertension for recoarctation and left ventricular enlargement. Moreover, relatively long aortic cross-clamp times and elevated catecholamine release in those patients may have contributed to a degree of reactive hypertension, not treatable with single-drug-therapy.

Undoubtedly the wide range of patient ages, various diagnoses, and different degrees of treatments for preoperative hypertension confound our study’s data. On the other hand, the heterogeneous group of pediatric and adult patients with native or re-coarctation in our study reflects the manifold peculiarity of coarctation in a tertiary care center. However, the treatment of reactive hypertension with either esmolol or sodium nitroprusside in moderate dosages or in combination effectively lessened postoperative activation effects of the sympathetic and renin–angiotensin systems. Thus, we recommend that both drugs be administered simultaneously if monotheraphy fails.
Acknowledgements

We would especially like to thank Daniela Moeske-Scholz for technical assistance and Carole Cürtén for editorial help with the manuscript.

References


Appendix A. ICVTS on-line discussion

Author: Dr. Enrico Aidala, Osp. Infantile “Regina Margherita”, Pediatric Cardiac Surgery, P.zza Polonia 94, Torino, 10126, Italy

Date: 25-Feb-2003 15:28

Message: In the postoperative period, nitroprusside, which donates nitric oxide groups to relax smooth muscle cells, is widely used to treat hypertension, with high efficacy and effect. However, in patients with coarctation, esmolol might be the first-choice drug. Due to postoperative stress answer, there is a release of high dosages of adrenergic hormones; the drug inhibits and downloads the adrenergic beta-receptors; it also reduces the parietal stress in the arterial vessels, a very useful action in the presence of a chronic vascular reactivity, as well as in case of acute reactivity in a damaged vessel (vascular surgery, aortic deissection). For the neonates, the immaturity of the orthosimpathic nervous system could be the cause of the low frequency of postoperative hypertension, as well as the cause of the higher dosages of catecholamines, compared to adults, often required in clinical practice.