OBSTETRICS

Haemodynamic effects of repeated doses of oxytocin during Caesarean delivery in healthy parturients

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Background. The haemodynamic effects of oxytocin 5 u have been described previously, but still some authors attribute these effects to the delivery itself. We studied the haemodynamic effects of two repeated doses of oxytocin i.v. in 20 healthy women during spinal anaesthesia for Caesarean delivery.

Methods. Data were obtained from a randomized controlled study of 80 pregnant women undergoing an elective Caesarean section. All women had an arterial line inserted, and LidCOPlus was used for measuring cardiac output (CO), stroke volume (SV), and systemic vascular resistance (SVR).

Results. Twenty women required a second bolus of oxytocin 5 u. Both the first and the second doses produced clinically and statistically significant haemodynamic changes, but the haemodynamic changes induced by the second dose were smaller than after the first dose. The mean maximal change in CO after the first and second doses were 94% (CI 70–117) and 42% (CI 33–52), respectively (P<0.0001), and for systolic arterial pressure 31% (CI 27–35) and 23% (CI 20–27), respectively (P=0.003).

Conclusions. An initial bolus of oxytocin 5 u produced prominent haemodynamic changes, whereas a second bolus produced smaller changes. This could be due to desensitization of endothelial oxytocin receptors.

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Oxytocin is the first choice drug for enhancing uterine contraction after delivery. There are oxytocin receptors in the uterus, and receptors have also been located in mammary, endothelial, and central nervous tissue as well.1 The effect of oxytocin on endothelial receptors produces a calcium-dependent vasodilatory effect via stimulation of the nitric oxide pathway.1 The substantial haemodynamic effect of oxytocin 5 u i.v. in healthy pregnant patients during spinal anaesthesia for Caesarean section has previously been published.2–5 In this study, we present data on the haemodynamic effects of two consecutive bolus doses of i.v. oxytocin in healthy parturients during elective Caesarean section.

Methods

Data were obtained from a randomized controlled study of 80 pregnant women undergoing an elective Caesarean section.5 The trial was approved by the Regional Committee for Medical Research Ethics of Southern Norway. The women gave written consent to participate in the study. All women had an arterial line inserted, and LidCOPlus (LiDCO, London, UK) was used for invasive monitoring of stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR).7 8 This monitor performs a beat-by-beat analysis of the arterial pressure wave to determine SV and other haemodynamic variables which are stored in the computer.
Women were given spinal anaesthesia with isobaric bupivacaine (7 or 10 mg) and sufentanil 4 μg with a prophylactic phenylephrine infusion or a placebo infusion. An i.v. bolus of oxytocin 5 u (Syntocinon, Novartis, Copenhagen, Denmark) was injected into a rapidly running i.v. line immediately after delivery. Twenty women required a second bolus of oxytocin 5 u. Ten of these women were given 7 mg and 10 were given 10 mg of spinal bupivacaine. Baseline haemodynamic measurement was defined as the mean value during the last 30 s before the injection of oxytocin. The differences in maximal haemodynamic changes of the first and the second doses in these 20 patients were analysed using SPSS statistical program version 15.0 (Statistical Package for Social Sciences Inc., Chicago, IL, USA) by paired t-test. Bonferroni’s correction (P/K; K, number of analyses) was performed to avoid type I error due to multiple outcome analyses. Hence, P-values <0.0125 (K=4) were regarded as statistically significant in the analyses of CO, SV, systolic arterial pressure (SAP), and SVR.

The haemodynamic data from each patient were downloaded as csv-files from the LiDCOplus-monitor. Construction of the data set was done using MatLab version R2007a (The MathWorks, Natick, MA, USA), where the beat-to-beat values were computed into average values every 10 s.

**Results**

Twenty women needed two doses of oxytocin 5 u. The haemodynamic effects of the first and second doses were clinically and statistically different from baseline (Fig. 1). The haemodynamic changes after the first dose were more prominent than after the second dose of oxytocin. Table 1 shows the haemodynamic changes for CO, SAP, SVR, and SV after the first and second doses of oxytocin, including P-values for the paired t-test. Mean CO increased from 7.2 to 13.8 litre min\(^{-1}\) after the first dose and from 6.9 to 9.8 litre min\(^{-1}\) after the second dose. Baseline was defined as the mean value during the last 30 s before the injection of oxytocin. When administering the second dose of oxytocin, the baseline was lower for SAP and for SVR. The mean time interval between the first and the second doses of oxytocin was 376 s (range 105–1009).

There were minor, and non-significant, differences in bleeding (495 vs 450 ml) and haemoglobin decrease (1.0 vs 0.7 g dl\(^{-1}\)) in these 20 patients compared with the other 60 patients in the study. Nine patients were given misoprostol 400 μg rectally, three patients had an infusion of oxytocin after delivery, and one patient had an intramyometrial injection of prostinfenem.

**Discussion**

Our data demonstrate the haemodynamic effects of oxytocin 5 u i.v. in healthy parturients during Caesarean section, confirming the results from previously published trials.\(^2–4\) Our findings also demonstrate that a second dose of i.v oxytocin 5 u given on average 6 min after delivery produced clinically significantly haemodynamic effects in the same direction as the first dose, but the effects are statistically significantly smaller than after the first dose. A recently published study giving oxytocin 10 u showed the same magnitude of haemodynamic effects in non-pregnant women as in pregnant women during Caesarean section.\(^5\) This documents that the circulatory changes of oxytocin after delivery really are caused by oxytocin, and are not due to the delivery itself as stated by some authors.\(^10\) Delivery may contribute to the circulatory changes, but the main effects are due to oxytocin. This was demonstrated by Thomas and colleagues\(^3\) comparing a bolus of oxytocin with an infusion. To examine the effect of delivery itself, one must design a study in which the oxytocin injection is delayed some minutes after delivery of the baby. An implication of the findings reported here is that administration of oxytocin 5 u as a bolus should probably be abandoned since the large haemodynamic effects could

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**Fig 1** The haemodynamic effects of two doses of oxytocin 5 u i.v. in 20 patients. Injection of oxytocin 5 u is administered at time=30 s. CO, cardiac output; SVR, systemic vascular resistance; SAP, systolic arterial pressure; SV, stroke volume. Oxy1, first dose of oxytocin 5 u. Oxy2, second dose of oxytocin 5 u.
be dangerous to vulnerable parturients. An infusion, or smaller repeated doses, might be a better choice.

The reduced effects of a second-dose oxytocin could be due to a decrease in endothelial receptor sensitivity. Desensitization of uterine oxytocin receptors has been described after continuous oxytocin infusion. Oxytocin-induced desensitization is concentration-dependent and is characterized by a reduction in the number of oxytocin binding sites on intact myometrial cells. Our findings of a clinically significant decrease in haemodynamic changes after a second oxytocin injection could indicate a concomitant desensitization of endothelial oxytocin receptors. The mean time interval between the two doses of oxytocin was ~6 min. The half-life of oxytocin is 5–12 min. This implies that half of the first dose is still present when the second dose is given, and could be part of the explanation for the observed reduced effect of a repeated dose of oxytocin. Assessment of uterine tone is difficult to quantify and it may be relevant to question the practice of giving a repeated bolus of oxytocin. On the basis of current evidence, it might be justified to change medication instead of giving a second dose of oxytocin. Phaneuf and colleagues have shown that oxytocin-induced desensitization does not affect the response to other agonists such as prostaglandins. In our department, we give misoprostol, a synthetic prostaglandin analogue, rectally (Cytotec, Pfizer, NY, USA).

In conclusion, this study confirms the haemodynamic effects after two repeated doses of oxytocin. The haemodynamic changes after the second dose are smaller compared with the first dose of oxytocin.

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5. Sartain JB, Barry JJ, Howat PW, McCormack DJ, Bryant M. Intravenous oxytocin bolus of 2 units is superior to 5 units during elective Caesarean section. *Br J Anaesth* 2008; 101: 822–6

### Table 1 Mean maximum changes in haemodynamic variables after oxytocin 5 u i.v. Values are presented as mean (95% CI). CO, cardiac output in litre min⁻¹; SAP, systolic arterial pressure in mm Hg; SVR, systemic vascular resistance in dyn s cm⁻⁵; SV, stroke volume in ml; HR, heart rate; %Change, percentage change from baseline; Maximum, mean maximum values in CO and SV; Minimum, mean minimum values in SAP and SVR. Paired t-test of maximal haemodynamic changes for the first and second dose oxytocin

<table>
<thead>
<tr>
<th>Variable</th>
<th>First dose</th>
<th>Second dose</th>
<th>Paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO Baseline</td>
<td>7.2 (6.1–8.4)</td>
<td>6.9 (5.8–8.0)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Maximum</td>
<td>13.8 (11.3–16.3)</td>
<td>9.8 (8.3–11.4)</td>
<td></td>
</tr>
<tr>
<td>%Change</td>
<td>94 (70–117)</td>
<td>42 (33–52)</td>
<td></td>
</tr>
<tr>
<td>SAP Baseline</td>
<td>132 (129–141)</td>
<td>116 (106–125)</td>
<td>P=0.003</td>
</tr>
<tr>
<td>Minimum</td>
<td>91 (83–100)</td>
<td>90 (79–100)</td>
<td></td>
</tr>
<tr>
<td>%Change</td>
<td>31 (27–35)</td>
<td>23 (20–27)</td>
<td></td>
</tr>
<tr>
<td>SVR Baseline</td>
<td>1032 (865–1199)</td>
<td>887 (732–1043)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Minimum</td>
<td>383 (319–447)</td>
<td>425 (402–512)</td>
<td></td>
</tr>
<tr>
<td>%Change</td>
<td>62 (57–67)</td>
<td>42 (38–46)</td>
<td></td>
</tr>
<tr>
<td>SV Baseline</td>
<td>85 (73–98)</td>
<td>84 (73–94)</td>
<td>P=0.0001</td>
</tr>
<tr>
<td>Maximum</td>
<td>124 (103–145)</td>
<td>103 (89–117)</td>
<td></td>
</tr>
<tr>
<td>%Change</td>
<td>45 (35–55)</td>
<td>22 (19–26)</td>
<td></td>
</tr>
<tr>
<td>HR Baseline</td>
<td>85 (78–91)</td>
<td>83 (77–90)</td>
<td>P=0.003</td>
</tr>
<tr>
<td>Maximum</td>
<td>119 (112–125)</td>
<td>101 (95–107)</td>
<td></td>
</tr>
<tr>
<td>%Change</td>
<td>42 (33–52)</td>
<td>23 (17–30)</td>
<td></td>
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