Oxytocin injection after Caesarean delivery: intravenous or intramyometrial?

Kevin C. Dennehy MB FFARCSI,
Ola P. Rosaeg MB FRCPC,
Nicholas J. Cicutti PhD,
Barbara Krepski RN,
Jacques P. Sylvain MD FRCSC*

Purpose: To determine, after Caesarean delivery, uterine contractility and blood pressure following intravenous (*iv*) and intramyometrial (*imy*) injection of oxytocin.

Methods: In a double-blind clinical trial 40 parturients scheduled for elective Caesarean section with spinal anaesthesia were randomized into two equal groups. One litre Ringer's lactate was administered *iv* before intrathecal injection of 1.7 ml bupivacaine 0.75% and 0.3 mg morphine. All patients received simultaneous *iv* and *imy* injections after removal of the placenta. Patients in Group 1 received 5 IU (10 IU·ml^{-1}) oxytocin *iv* and 2 ml saline *imy*; Group 2 patients received 0.5 ml saline *iv* and 20 IU oxytocin into the myometrium. Baseline systolic blood pressure (SBP) and heart rate were measured before delivery and at one minute intervals for 15 min after injection of study solutions. Uterine contractility was assessed at 1, 2, 4, 6, 8, 10 and 15 min after oxytocin injection. Haemoglobin concentration before surgery and on first post-operative day was also recorded.

Results: Mean decrease in systolic blood pressure (SBP) one minute after oxytocin was 8.4 mmHg in Group 1 *vs* 14.6 mmHg in Group 2 ($P < 0.001$). Systolic blood pressure returned to baseline two minutes after oxytocin in Group 1 and after three minutes in Group 2. Uterine contractility and change in haemoglobin concentration were similar in both groups.

Conclusion: Intramyometrial administration of 20 IU oxytocin after Caesarean delivery is associated with more severe hypotension than is *iv* injection of 5 IU oxytocin. Route of oxytocin injection did not affect uterine tone.

Objectif : Déterminer la contractilité utérine et la tension artérielle qui suivent une injection intraveineuse (iv) et intramyométriale (imy) d'ocytocine après un accouchement par césarienne.

Méthode : Lors d'un essai clinique en double aveugle, 40 parturientes devant subir une césarienne élective et recevoir une anesthésie péridurale ont été réparties de façon aléatoire en deux groupes égaux. Un litre de lactate de Ringer a été administré iv avant une injection intrathécale de 1,7 ml de bupivacaïne à 0,75 % et 0,3 mg de morphine. Toutes les patientes ont reçu des injections simultanées iv et imy après l'extraction du placenta. Les patientes du groupe 1 ont reçu 5 UI (10 UI·ml^{-1}) d'ocytocine iv et 2 ml de solution salée imy; les patientes du groupe 2 ont reçu 0,5 ml de solution salée iv et 20 UI d'ocytocine imy. La tension artérielle systolique (TAS) de base et la fréquence cardiaque ont été mesurées avant l'accouchement et à intervalles d'une minute pendant 15 minutes après l'injection des solutions-test. La contractilité utérine a été évaluée à 1, 2, 4, 6, 8, 10 et 15 minutes après l'injection d'ocytocine. On a aussi enregistré la concentration d'hémoglobine avant la chirurgie et le premier jour postopératoire.

Résultats : La baisse moyenne de la tension artérielle systolique (TAS), une minute après l'injection d'ocytocine, était de 8,4 mmHg dans le groupe 1 *vs* 14,6 mmHg dans le groupe 2 ($P < 0,001$). Également après l'ocytocine, il a fallu deux minutes pour le groupe 1 et trois minutes pour le groupe 2 avant de retrouver la tension artérielle de base. La contractilité utérine et le changement dans la concentration d'hémoglobine ont été similaires dans les deux groupes.

Conclusion : L'administration intramyométriale de 20 UI d'ocytocine après une césarienne est associée à une hypotension plus sévère qu'avec une injection iv de 5 UI d'ocytocine. La voie d'administration de l'ocytocine n'a pas affecté la tonicité utérine.

From the Department of Anaesthesia and the Department of Obstetrics and Gynaecology,* Ottawa Hospital, University of Ottawa, 1053 Carling Avenue, Ottawa, Ontario, K1Y 4E9 Canada.
Address correspondence to: Dr. O.P. Rosaeg. Phone: 613-761-4169; Fax: 613-761-5209; E-mail: norse@cyberus.ca
Accepted for publication March 21, 1998.

OXYTOCIN is routinely administered *iv* after Caesarean section to promote uterine contraction, thus reducing blood loss from the placental site. Intravenous bolus injection of oxytocin is associated with abrupt onset of transient hypotension,[1-4] which can be particularly harmful in parturients with hypovolaemia or cardiac disease. Direct intramyometrial injection of oxytocic drugs also increases uterine contractility. Intramyometrial injection of 250 μg prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is effective in the treatment of uterine atony.[5,6] Catanzarite[7] studied the effect of 20 IU intramyometrial oxytocin after elective Caesarean section and determined that blood loss was similar to that observed in patients who had received intramyometrial 125 μg $PGF_{2\alpha}$. The haemodynamic consequences of intramyometrial oxytocin administration have not been studied. Also, the comparative efficacy of *imy* and *iv* oxytocin to increase uterine tone has not been determined. We therefore decided to investigate, in a prospective randomized double blind fashion, the haemodynamic changes and uterine contractility following intramyometrial and intravenous administration of oxytocin after elective Caesarean delivery with spinal anaesthesia.

Methods

The study protocol was approved by the institutional Research Ethics Committee. Written informed consent was obtained from 40 ASA I or II women with singleton fetus scheduled for elective Caesarean section at term (≥ 37 wk gestation). Exclusion criteria included age <18 yr, contraindication to spinal anaesthesia, polyhydramnios, placenta praevia, uterine fibroids, hypertension or cardiac disease. Also, patients who received *iv* ephedrine within 10 min of delivery were excluded from the study.

Parturients were assigned to one of two study groups; intravenous oxytocin (Group 1) or intramyometrial oxytocin (Group 2) according to a computer generated series of random numbers. No premedication was given except 30 ml 0.3M sodium citrate *po*. Baseline systolic blood pressure and heart rate were obtained prior to insertion of an *iv* cannula (BL-1). One litre Ringer's lactate solution *iv* was infused before intrathecal injection of 1.7 ml bupivacaine 0.75% and 0.3 ml (mg) of preservative-free morphine. Spinal anaesthesia was induced in the sitting position at the L_{2-3} or L_{3-4} interspace using a #27 Whitacre spinal needle. Intra-operative monitoring included ECG, pulse oximetry and automated non-invasive blood pressure monitoring. All parturients received 3 $L \cdot min^{-1}$ O_2 by nasal cannula until delivery of the infant. The patient was positioned supine with left uterine displacement with a standard device immediately after intrathecal injection. Systolic blood pressure and heart rate were also recorded prior to uterine incision (BL-2). Ephedrine was given in 5 mg increments *iv* before delivery if systolic blood pressure (SBP) decreased to <100 mmHg. The hospital pharmacy prepared the syringes containing the study solutions under aseptic conditions according to the random table and delivered them to the delivery room in a plastic bag. A 3 ml syringe with a #22 needle contained 2 ml of study solution for *imy* administration. The second 1.0 ml syringe contained 0.5 ml of study solution for *iv* injection. All parturients were given two simultaneous injections. The injections were conducted in a double blind fashion where neither the attending anaesthetist or obstetrician had knowledge of the content of the syringes. Patients in the *imy* group received 2 ml oxytocin (10 $IU \cdot ml^{-1}$) into the myometrium of the uterine fundus and 0.5 ml sterile saline *iv*. Conversely, parturients in the *iv* group received 2 ml sterile saline into the myometrium and 0.5 ml (10 $IU \cdot ml^{-1}$) oxytocin *iv*. Intramyometrial and intravenous injections of study solutions were given immediately after expulsion of the placenta. The obstetrician assessed uterine tone on a 10-point linear analog scale[8] (0 = flaccid, 10 = maximum contraction) at 1, 2, 4, 6, 8, 10, 15 min after injection of drug. Systolic blood pressure and heart rate were recorded at one minute intervals for 15 min (end of study period) after injection of study solutions. Ephedrine was only administered after Caesarean delivery if SBP was >25% below BL-2 at two subsequent one minute interval measurements. Times of intrathecal injection, skin incision, uterine incision, uterine closure, and skin closure (timelines) were recorded. The volume of Ringer's lactate infused before injection of study drugs was noted. We also recorded the total volume of crystalloid solution infused until the end of the study period. Pre-operative (within one week of delivery) haemoglobin concentrations were recorded as well as the values obtained on the first post-operative day.

Demographic data, change in haemoglobin concentration and timelines were analysed using Student's t test. Haemodynamic measurements and uterine tone were analysed using repeated measures analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant.

Results

One patient did not complete the study protocol because the attending anaesthetist was unable to locate the subarachnoid space and she, therefore, received general anaesthesia for Caesarean section. There was no difference between groups in demographic data (Table I). There was also no difference between groups

TABLE I Demographic data

Group	IV (*n* = 20)	IMY (*n* = 19)
Age (yr)	30.6 ± 4.8	32.4 ± 4.7
Gravida	2.3 ± 1.1	2.3 ± 1.1
Gestation (wk)	38.5 ± .8	38.3 ± .9
Neonatal weight (g)	3404 ± 536.3	3197.3 ± 385.3
Placental weight (g)	721.3 ± 167.9	739.2 ± 163

Mean ± SD

TABLE II Infused volume of Ringer's lactate

Group	IV (*n* = 20)	IMY (*n* = 19)
Before oxytocin injection (ml)	1660 ± 243.6	1688 ± 130.8
Total intra-op volume (ml)	2238.7 ± 422.1	2121 ± 239.9

Mean ± SD

TABLE III Timelines

Group	IV (*n* = 20)	IMY (*n* = 19)
Intrathecal injection to skin incision (min)	16.2 ± 3.2	16.4 ± 4.9
Uterine incision to uterine closure (min)	13.5 ± 3.6	11.5 ± 3.2
Skin incision to skin closure (min)	36.2 ± 10.5	31.9 ± 9.7

Mean ± SD

TABLE IV Haemoglobin concentration ($g \cdot L^{-1}$)

Group	IV (*n* = 20)	IMY (*n* = 19)
Pre-operative	118.9 ± 13.8	121.4 ± 8.8
1st post-operative day	107.7 ± 13.4	109.8 ± 10.4

Mean ± SD

in the volume of Ringer's lactate infused before injection of oxytocin or the recorded timelines during surgery (Tables II, III).

The maximum decrease in SBP occurred at one minute after oxytocin injection in both groups. The mean SBP was 14.6 mmHg (13.0 %) lower than BL-2 (Figure 1A) after *imy* administration of oxytocin in Group 2 patients. In contrast, mean SBP decreased 8.4 mmHg (7.4%) after *iv* oxytocin injection at this time interval. Systolic blood pressure was also lower in Group 2 than Group 1 at the three and four minute intervals after oxytocin injection (Figure 1A). Heart rate increased one minute after oxytocin administration in both groups, but the increase in heart rate was higher in patients in Group 2 ($P < 0.05$, Figure 1B). There was no difference between groups in uterine tone after oxytocin injection (Figure 2), or change in haemoglobin concentration from pre-operative values (Table IV). No patients received supplementary oxytocin or ephedrine *iv* during the 15 min period after oxytocin injection.

Discussion

The results of our investigation indicate that *imy* injection of 20 IU oxytocin after Caesarean delivery under spinal anaesthesia is associated with a temporary decrease in blood pressure and with an increase in heart rate. The decrease in blood pressure from baseline values was less after *iv* than after *imy* administration. In addition, return to baseline SBP (BL-2) occurred sooner after *iv* than after *imy* injection of oxytocin. Uterine contractility after 20 IU oxytocin *imy* was similar to that observed after 5 IU oxytocin *iv*. Furthermore, there was no difference between study groups in haemoglobin concentration 24 hr after Caesarean section, indicating that there was no difference between the groups in the amount of blood lost during surgery. We did not attempt to estimate blood loss, as this is notoriously difficult considering admixture of amniotic fluid in suction apparatus and bleeding from sources other than the placental site.[9]

It is well known that *iv* bolus injection of oxytocin may result in short-lived hypotension in non-pregnant patients,[2,3] during pregnancy[2,4] and after Caesarean delivery.[1] The aetiology of the observed haemodynamic changes is controversial and most likely multi-factorial. Studies in intact animals indicate that administration of oxytocin results in peripheral vasodilatation, resulting in a decreased mean arterial pressure with associated increase in heart rate and cardiac output.[10] Some investigators have observed a biphasic change in blood pressure; an initial decrease followed by an increase in mean arterial pressure.[11] However, these studies were performed using general anaesthesia and oxytocin solutions containing preservatives that have important cardiovascular effects. Jahr *et al.*[12] observed a peripheral vasodilatory effect in rats after administration of chlorobutanol, which is a commonly used preservative in commercial oxytocin solutions. Rosaeg *et al.*[13] showed that chlorobutanol had a negative inotropic effect on a human *in vitro* atrial preparation. Pure oxytocin has been shown to have positive chronotropic and inotropic effects in amphibians, reptiles and mammals.[14–16] These studies indicate that the observed increase in heart rate and cardiac output may also be the result of a direct cardiac effect, not merely a reflex response to peripheral vasodilatation. Pure oxytocin is an arteriolar vasoconstrictor in animals,[17] and also causes constriction of the human umbilical and cerebral vasculature.[18,19] In addition, oxytocin plays a role in the central control of cardiovascular function. Petty *et al.*[20]

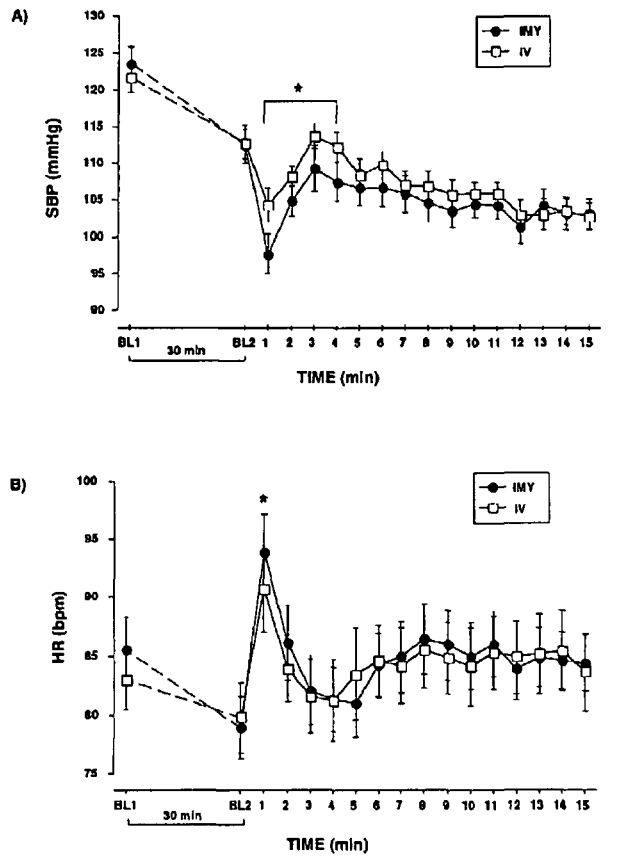

FIGURE 1 Graphical comparison of haemodynamic variables in the *imy* oxytocin (Group 1) and *iv* oxytocin (Group 2). Time interval between BL-1 and BL-2 was approximately 30 min in both groups. Values are mean ± SD. A) Significant reduction in SBP observed in *imy* group compared to *iv* group over initial four min after oxytocin injection. B) Significant increase in HR was shown at 1 min following oxytocin administration in both groups. * For both Figure 1A and 1B $P < 0.05$ between groups.

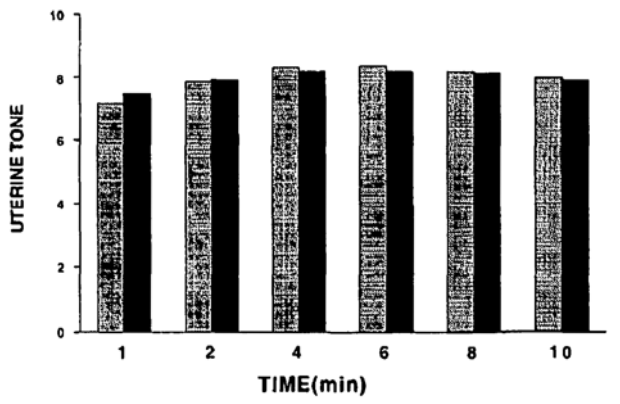

FIGURE 2 Uterine tone assessment using a 10-point linear analog scale (0 = flaccid, 10 = maximum contraction). Grey bars represent *imy* oxytocin (Group 1) and black bars represent *iv* oxytocin (Group 2). No significant difference was observed between groups over time.

determined that oxytocin decreased the sensitivity of the baroreflex in conscious rats. Oxytocin containing preganglionic nerve fibres originating in the hypothalamus also extend to the intermediolateral aspect of the spinal cord,[21] the amygdala[22] and stellate ganglion.[23] Thus, oxytocin may play a role in modulating autonomic control of the heart. In summary, there is no evidence that oxytocin *per se* is a direct negative inotropic drug or causes peripheral vasodilatation. Rather, the temporary hypotensive effect observed after *imy* or *iv* bolus administration of commercial oxytocin solution may largely be due to the negative inotropic and vasodilatory effect of the preservative chlorobutanol. We did not expect to find that 20 IU oxytocin *imy* to be associated with more severe hypotension than following 5 IU oxytocin *iv*. The most likely explanation for this finding is that *imy* oxytocin injection results in extensive, rapid absorption of oxytocin from the myometrium into the systemic circulation.

Blood loss during Caesarean delivery occurs from incision through the abdominal wall, myometrium and the placental bed. Oxytocin is commonly administered after Caesarean delivery to promote uterine contraction, thus reducing blood loss from the myometrium and the placental insertion site. Uterine atony may result in severe post-partum haemorrhage. Effective pharmacological treatment of uterine atony is often achieved by an intramyometrial injection of $PGF_{2\alpha}$, 250 µg.[5,6] Catanzarite[7] did not find any difference in estimated blood loss during elective Caesarean section between parturients who received 20 IU oxytocin *imy* and women who received 125 µg intramyometrial $PGF_{2\alpha}$. However, both study groups also received *iv* oxytocin which might have masked any difference in uterotonic effect between intramyometrial oxytocin and $PGF_{2\alpha}$. Furthermore, a prospective, randomized study of intravenous 20 IU oxytocin and intramyometrial $PGF_{2\alpha}$ 125 µg did not find any difference in blood loss during elective Caesarean delivery.[24] Sarna *et al.*[25] determined that uterine contractility and estimated blood loss was similar following 5 or 20 IU of oxytocin *iv*. Although this study did not determine the minimal effective dose of *iv* oxytocin after Caesarean delivery, their data suggest that it is unnecessary to administer more than 5 IU oxytocin *iv* after Caesarean delivery with neuraxial anaesthesia. A dose response study of *imy* oxytocin administration after Caesarean section is also warranted considering the results of our investigation.

Our data indicate that 20 IU oxytocin *imy* results in more severe transient hypotension than does 5 IU oxytocin *iv* after elective Caesarean delivery. In addition, *iv* and *imy* injections of oxytocin result in similar, effective uterine contraction after Caesarean delivery.

In conclusion, there is no clinical advantage associated with administration of oxytocin by the intramyometrial route rather than by conventional *iv* injection. Finally, we caution against the use of intramyometrial 20 IU oxytocin in the treatment of uterine atony since a deleterious decrease in blood pressure may ensue in a patient who is hypovolaemic as a result of post-partum haemorrhage.

References

1 *Andersen TW, De Padua CB, Stenger V, Prystowsky H.* Cardiovascular effects of rapid intravenous injection of synthetic oxytocin during elective cesarean section. Clin Pharm Ther 1965; 6: 345–9.

2 *Hendricks CH, Brenner WE.* Cardiovascular effects of oxytocic drugs used post partum. Am J Obstet Gynecol 1970; 108: 751–60.

3 *Johnstone M.* The cardiovascular effects of oxytocic drugs. Br J Anaesth 1972; 44: 826–33.

4 *Weis FR Jr, Markello R, Mo B, Bochiechio P.* Cardiovascular effects of oxytocin. Obstet Gynecol 1975; 46: 211–4.

5 *Hayashi RH, Castillo MS, Noah ML.* Management of severe postpartum hemorrhage due to uterine atony using an analogue of prostaglandin $F_{2\alpha}$. Obstet Gynecol 1981; 58: 426–9.

6 *Oleen MA, Mariano JP.* Controlling refractory atonic postpartum hemorrhage with Hemabate sterile solution. Am J Obstet Gynecol 1990; 162: 205–8.

7 *Catanzarite VA.* Prophylactic intramyometrial carboprost tromethamine does not substantially reduce blood loss relative to intramyometrial oxytocin at routine cesarean section. Am J Perinatol 1990; 7: 39–42.

8 *Ghaly RG, Flynn RJ, Moore J.* Isoflurane as an alternative to halothane for Caesarean section. Anaesthesia 1988; 43: 5–7.

9 *Duthie SJ, Ghosh A, Ng A, Ho PC.* Intra-operative blood loss during elective lower segment Caesarean section. Br J Obstet Gynaecol 1992; 99: 364–7.

10 *Nakano J, Fisher RD.* Studies on the cardiovascular effects of synthetic oxytocin. J Pharmacol Exp Ther 1963; 142: 206–14.

11 *Desiderio MA, Hanson KM.* Splanchnic vascular effects of pharmacologic doses of oxytocin in the canine (41086). Proc Soc Exp Biol Med 1981; 166: 432–7.

12 *Jahr JS, Holton RH, Feng C-J.* Effect of desmopressin acetate on hindlimb perfusion pressure in rats: what is the mechanism? Anesth Analg 1992; 75: 411–5.

13 *Rosaeg OP, Cicutti NJ, Labow RS.* The effect of oxytocin on the contractile force of human atrial trabeculae. Anesth Analg 1998; 86: 40–4.

14 *Chiu KW, Lee YC, Pang PKT.* Neurohypophysial hormones and cardiac activity in the frog, *Rana tigrina*, and in the snake, *Ptyas mucosa*. Gen Comp Endocrinol 1990; 78: 150–4.

15 *Aonuma S, Kohama Y, Akai K, et al.* Effects of oxytocin on beating properties, myosin ATPase activity and macromolecular synthesis of rat myocardial cells in culture. Chem Pharm Bull 1979; 27: 1857–63.

16 *Coulson CC, Thorp JM Jr, Mayer DC, Cefalo RC.* Central hemodynamic effects of oxytocin and interaction with magnesium and pregnancy in the isolated perfused rat heart. Am J Obstet Gynecol 1997; 177: 91–3.

17 *Altura BM, Altura BT.* Vascular smooth muscle and neurohypophyseal hormones. Federation Proceedings 1977; 36: 1853–60.

18 *Altura BM.* Humoral, hormonal, and myogenic mechanisms in microcirculatory regulation. *In*: Kaley G, Altura BM (Eds.). Microcirculation, Vol. II. Baltimore: University Park Press, 1978: 431–502.

19 *Abrams GM, Nilaver G, Recht LR, Haldar J, Zimmerman EA.* Hypothalamic oxytocin: a cerebral modulator in man? Neurology 1985; 35: 1046–9.

20 *Petty MA, Lang RE, Unger T, Ganten D.* The cardiovascular effects of oxytocin in conscious male rats. Eur J Pharamacol 1985; 112: 203–10.

21 *Swanson LW, McKellar S.* The distribution of oxytocin and neurophysin-stained fibers in the spinal cord of the rat and monkey. J Comp Neurol 1979; 188: 87–106.

22 *Roozendaal B, Schoorlemmer GHM, Koolhaas JM, Bohus B.* Cardiac, neuroendocrine, and behavioral effects of central amygdaloid vasopressinergic and oxytocinergic mechanisms under stress-free conditions in rats. Brain Res Bull 1993; 32: 573–9.

23 *Jansen ASP, Wessendorf MW, Loewy AD.* Transneuronal labeling of CNS neuropeptide and monoamine neurons after pseudorabies virus injections into the stellate ganglion. Brain Res 1995; 683: 1–24.

24 *Chou MM, MacKenzie IZ.* A prospective, double-blind, randomized comparison of prophylactic intramyometrial 15-methyl prostaglandin $F_{2\alpha}$, 125 micrograms, and intravenous oxytocin, 20 units, for the control of blood loss at elective cesarean section. Am J Obstet Gynecol 1994; 171: 1356–60.

25 *Sarna MC, Soni AK, Gomez M, Oriol NE.* Intravenous oxytocin in patients undergoing elective cesarean section. Anesth Analg 1997; 84: 753–6.