

## OBSTETRICS

# Intravenous oxytocin bolus of 2 units is superior to 5 units during elective Caesarean section

J. B. Sartain<sup>1\*</sup>, J. J. Barry<sup>1</sup>, P. W. Howat<sup>2</sup>, D. I. McCormack<sup>3</sup> and M. Bryant<sup>4</sup>

<sup>1</sup>Department of Anaesthesia, Intensive Care and Perioperative Medicine and <sup>2</sup>Department of Obstetrics and Gynaecology, Cairns Base Hospital, The Esplanade, Cairns, QLD 4870, Australia.

<sup>3</sup>Department of Anaesthesia, Mater Health Services Brisbane, South Brisbane, QLD 4101, Australia. <sup>4</sup>Department of Anaesthesia and Perioperative Medicine, Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia

\*Corresponding author. E-mail: james\_sartain@health.qld.gov.au

**Background.** The optimal dose of oxytocin at Caesarean section is unclear. Oxytocin may cause adverse cardiovascular effects, including tachycardia and hypotension, whereas an inadequate dose can result in increased uterine bleeding. We compared the effects of two doses of oxytocin in a randomized double-blind trial.

**Methods.** Eighty patients undergoing elective Caesarean section received an i.v. bolus of either 2 or 5 units (u) of oxytocin after delivery, followed by an oxytocin infusion of 10 u h<sup>-1</sup>. All received combined spinal–epidural anaesthesia with arterial pressure maintained by a phenylephrine infusion. We compared changes in heart rate (HR), mean arterial pressure (MAP), blood loss, uterine tone, the need for additional uterotonic drugs, and emetic symptoms.

**Results.** There was a greater increase in mean (SD) HR in patients who received 5 u of oxytocin [32 (17) beats min<sup>-1</sup>] than in those who received 2 u [24 (13) beats min<sup>-1</sup>] ( $P=0.015$ ). There was a larger decrease in MAP in patients who received 5 u [13 (15) mm Hg] than in those who received 2 u [6 (10) mm Hg] ( $P=0.030$ ). The frequency of nausea and antiemetic use was higher after 5 u (32.5%) than 2 u (5%) ( $P=0.003$ ). There were no differences in blood loss, uterine tone, or requests for additional uterotonic drugs (17.5% in both groups).

**Conclusions.** In elective Caesarean section, a 2 u bolus of oxytocin results in less haemodynamic change than 5 u, with less nausea and no difference in the need for additional uterotronics.

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Although oxytocin is used to aid uterine contraction after delivery at Caesarean section, the optimal dose is unclear.<sup>1–3</sup> Oxytocin causes cardiovascular effects, including tachycardia, hypotension, and ST changes,<sup>1,2,4</sup> and the i.v. administration of 10 units (u) of oxytocin has been reported to cause cardiovascular collapse and death.<sup>5</sup> Although 5 u is the recommended dose in the UK and Australia,<sup>6</sup> the minimum effective bolus dose for 90% of patients (ED90) at elective Caesarean section has recently been estimated to be as low as 0.35 u.<sup>7</sup> However, it appears that many practitioners remain unconvinced.

A recent UK survey of 365 obstetricians and anaesthetists found that nearly all gave an initial ‘slow bolus’ of at least 5 u,<sup>8</sup> followed by the selective use of an oxytocin infusion, most commonly at 10 u h<sup>-1</sup>.

Our clinical impression has been that a smaller bolus of 2 u oxytocin, followed by a routine infusion, produces adequate uterine contraction with fewer adverse effects than a larger bolus. So in the present study, we compared the haemodynamic and adverse effects of 2 u, compared with 5 u of oxytocin, when both were followed by an oxytocin infusion of 10 u h<sup>-1</sup>.

## Methods

The study was approved by the ethics committee of the Cairns Base Hospital. After written informed consent, 80 women undergoing elective Caesarean section under regional anaesthesia received either 2 or 5 u of i.v. oxytocin after delivery in a randomized double-blind fashion. Patients at increased risk of uterine atony or excessive bleeding (more than two previous Caesarean sections, a history of previous post-partum haemorrhage, known placenta praevia or accreta, twin pregnancy, and polyhydramnios) or cardiovascular instability (pre-eclampsia or essential hypertension) were excluded.

All patients received famotidine 40 mg both the night before and the morning of surgery. In the operating theatre, i.v. access was secured, then pulse oximetry, ECG, and non-invasive blood pressure (NIBP) monitoring were commenced (Datex-Ohmeda S/5 Anesthesia Monitor). All patients received a combined spinal–epidural anaesthetic in the sitting position with hyperbaric bupivacaine 0.5% (2.3 ml) and fentanyl 10 µg given intrathecally. After securing the epidural catheter, patients were laid supine with a wedge under the right flank to achieve a leftward tilt of 15°. One litre of Hartmann's solution was then rapidly infused over 10–15 min, with further i.v. fluids given at the discretion of the anaesthetist. A phenylephrine solution 100 µg ml<sup>-1</sup> was infused initially at 30 ml h<sup>-1</sup> (3 mg h<sup>-1</sup>) and titrated to maintain mean arterial pressure (MAP) within 10% of the level before anaesthesia.<sup>9</sup> Measurement of NIBP was taken at 1 min intervals from when the patient was laid supine until 10 min after delivery. Surgery was allowed once the neuraxial block height had reached T4 to cold perception using ice. Additional analgesic or anxiolytic medications were given at the discretion of the anaesthetist.

After delivery of the baby and cord clamping, the anaesthetist gave a 5 ml i.v. bolus of pre-prepared oxytocin (Syntocinon, Novartis), over 5–10 s. From a series of random numbers in sealed envelopes, either 2 or 5 u had been premixed in saline by a doctor not involved in the care of the patient or any data recordings, so that each anaesthetist and obstetrician was blinded to the oxytocin dose. Immediately after the bolus, a separate infusion of oxytocin 40 u in 1 litre of Hartmann's solution was commenced at 250 ml h<sup>-1</sup> (i.e. 10 u h<sup>-1</sup> for 4 h).

In addition to minutely measures of NIBP and heart rate (HR), the maximum HR after the oxytocin bolus was recorded (the Datex monitor displays a 10 s median HR, updated every second). The last measurement of NIBP and HR before giving oxytocin was recorded as a baseline for subsequent changes.

The placenta was delivered by controlled cord traction. Uterine tone was assessed by the obstetrician at 5, 10, 15, and 20 min on a five-point scale, where 1=atonic; 2=partial but inadequate contraction; 3=adequate contraction; 4=well contracted; and 5=very well contracted.

Additional uterotonic drugs, if requested by the obstetrician, were administered in the following order: 5 u oxytocin, 10 u oxytocin, ergometrine 0.25 mg (all i.v.), then intramyometrial prostaglandin. Blood loss was estimated by visual assessment of suction bottles and drapes.

The occurrence of nausea or vomiting, both before and after the oxytocin bolus, was assessed by patient report and frequent direct questioning until the patient left the operating theatre, and recorded as a binary outcome (yes or no). Emetic symptoms were treated by correction of any hypotension, then if necessary with rescue antiemetics (one or more of i.v. metoclopramide 10 mg, ondansetron 4 mg, or droperidol 0.5–1 mg).

From previous studies,<sup>1,2</sup> it was predicted that changes in HR would be more reliable than changes in MAP when using non-invasive monitoring, so the primary outcome was the maximum change in HR after oxytocin. Sample size calculations were based on the data from Thomas and colleagues,<sup>1</sup> that is, a HR difference between the groups of 7 beats min<sup>-1</sup>, with a standard deviation of 11. So at a power of 0.8 and  $P<0.05$ , 40 patients were required for each group for an unpaired Student's *t*-test. Additionally, Welch's *t*-test was used for parametric data with unequal variances; non-parametric data were analysed with a Mann–Whitney *U*-test; incident data were analysed with a Fisher exact test; and a paired *t*-test or Wilcoxon signed-rank test was used for comparing before-and-after changes within a group. Data were entered in an Access 2002 database and analysed using SigmaStat 3.5 and SigmaPlot 10.0.

## Results

Eighty women were randomized and all completed the study. The patient characteristics of the two groups were similar, with no significant differences in vasopressor or antiemetic requirements before oxytocin was given (Table 1). The requirements for additional analgesia during surgery were equal (eight in each group).

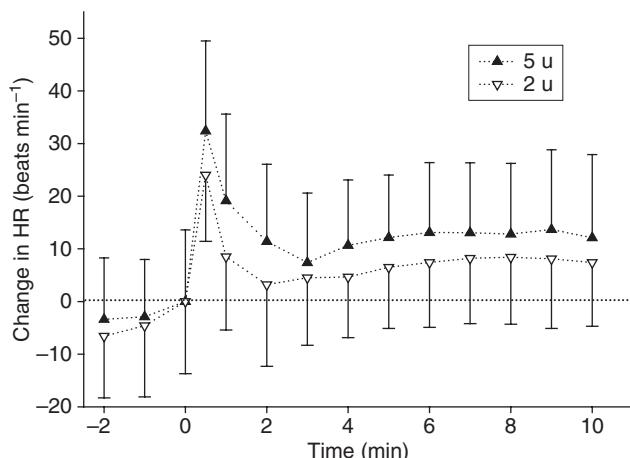
After oxytocin, there was a significant increase from baseline in HR ( $P<0.001$  for both groups). The greatest change in HR usually occurred <1 min after the oxytocin bolus,

**Table 1** Patient characteristics and treatments before oxytocin bolus. Data are presented as number, mean (range) for age, mean (SD), or median (range)

	2 u (n=40)	5 u (n=40)	P-value
Age (yr)	30.8 (20–40)	30.9 (21–41)	0.889
Weight (kg)	79.3 (19.9)	77.6 (13.4)	0.679
Race: Caucasian	31	31	1.000
Parity	1.5 (0–6)	1.5 (0–7)	0.748
Nausea	5	8	0.546
Antiemetic treatment	2	3	1.000
Phenylephrine dose (µg)	1000 (300–2400)	800 (200–2100)	0.119
HR before oxytocin (beats min <sup>-1</sup> )	76 (14)	72 (14)	0.285
MAP before oxytocin (mm Hg)	93 (10)	91 (11)	0.432

**Table 2** Outcomes after oxytocin bolus. Data are presented as number, mean (SD), or median (range). ‘Fluids given’ includes the amount before oxytocin; HR data are before 1 min; MAP data are at 1 min

	2 u (n=40)	5 u (n=40)	P-value
Fluids given (ml)	2000 (1000–3000)	2000 (1000–6500)	0.094
Phenylephrine dose (μg)	300 (0–2200)	400 (0–3200)	0.849
Increase in HR (beats min <sup>-1</sup> )	24 (13)	32 (17)	0.015
Decrease in MAP (mm Hg)	6 (10)	13 (15)	0.030
Nausea	2	13	0.003
Vomiting	1	6	0.108
Antiemetic treatment	2	13	0.003
Blood loss	500 (150–1200)	500 (200–2000)	0.889
Additional uterotonic treatment at 5 min	2	3	1.000
Additional uterotonic treatment overall	7	7	1.000

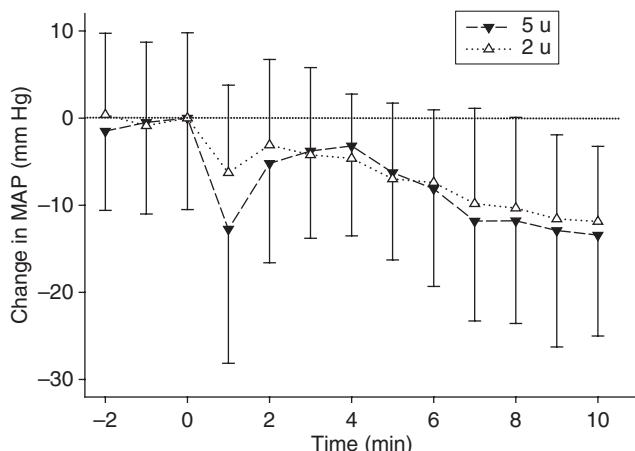


**Fig 1** Change in HR after oxytocin bolus (time 0). Data points shown are mean and SD.

and was greater in the 5 u than the 2 u group (Table 2). Twenty-three patients (57.5%) who received 5 u had a HR increase of over 30 beats min<sup>-1</sup> compared with 11 (27.5%) who received 2 u ( $P=0.012$ ). After an initial recovery, the HR again increased significantly from baseline after 4 min in the 5 u group and after 5 min in the 2 u group (Fig. 1).

There was a significant decrease in MAP from baseline at 1 min in both groups ( $P\leq 0.005$ ), which was greater in the 5 u than the 2 u group (Table 2). Six patients (15%) who received 5 u had a decrease in MAP of more than 30 mm Hg compared with none who received 2 u ( $P=0.026$ ). After an initial recovery, the MAP again decreased significantly from baseline in both groups after 5 min (Fig. 2). There were no differences between the groups for total fluids given during surgery or the dose of phenylephrine after oxytocin (Table 2).

Thirteen patients (32.5%) reported nausea and received antiemetic treatment after 5 u oxytocin compared with two (5%) who received 2 u (Table 2). The difference in vomiting frequency was not statistically significant (Table 2).



**Fig 2** Change in MAP after oxytocin bolus (time 0). Data points shown are mean and SD.

There were no differences between the groups in blood loss, uterine tone at any measurement time, or in the requirement for additional uterotonic drugs (Table 2). Cumulatively more patients required uterotonic treatment over the study period: five patients (6.25%) needed additional uterotonics at 5 min; by 20 min, 14 patients (17.5%) had required treatment (Table 2). A total of nine doses of additional uterotonics were required in the 2 u group, compared with 17 doses in the 5 u group. However, eight of these were for two patients in the 5 u group, who also needed surgical treatment for persistent hypotonia and excessive blood loss. In one patient, who needed a B-lynch suture, the reason for the lack of response was unclear; in the second, who required hysterectomy, placenta accreta was later found on histology. Although results from the latter patient were included on an intention-to-treat basis, the conclusions of the study were unaffected if her results were omitted.

## Discussion

Although maternal haemodynamic changes after delivery at Caesarean section have many potential causes, including removal of aorto-caval compression, autotransfusion from uterine contraction, blood loss, vasopressors, and emotional excitement, previous studies have shown that uterotonic drugs are a dominant factor.<sup>1,2</sup> The most consistent cardiovascular changes observed after oxytocin are a dose-related decrease in arterial pressure due to peripheral vasodilation, with a compensatory increase in HR and cardiac output.<sup>1,2,10,11</sup>

We found that an i.v. bolus of 2 u oxytocin at Caesarean section resulted in less haemodynamic change than a 5 u bolus. The increase in HR was significantly greater and more prolonged after 5 u than after 2 u. The mean decrease in MAP was also significantly greater in the 5 u group, with six patients (15%) sustaining a decrease of more than 30 mm Hg, compared with none in

the 2 u group. Thomas and colleagues,<sup>1</sup> using invasive pressure monitoring, found a decrease in MAP of 14 mm Hg at 1 min after a 5 u bolus, but with a maximum decrease of 27 mm Hg at 25 s. We observed an almost identical mean decrease of 13 mm Hg at 1 min after 5 u when measured by NIBP, so it is likely that the maximum decrease in MAP was underestimated in our study. It is also of note that after an initial recovery, both HR and MAP later differed significantly from baseline in both groups. This may be explained largely by vasodilation from the ongoing oxytocin infusion and the lower dose of phenylephrine used after delivery.

The clinical importance of haemodynamic changes after oxytocin remains unclear.<sup>2-4</sup> Although maternal death has been attributed to the effects of a 10 u bolus of oxytocin,<sup>5</sup> catastrophic outcomes appear rare. The (usually transient) haemodynamic effects may only be important in the event of pre-existing heart disease or hypovolaemia, when patients may be unable to compensate for the sudden vasodilation.<sup>4,5</sup> As we found significant changes even after a 2 u bolus, an even smaller initial bolus, or an oxytocin infusion alone, might be a safer option in these situations.

One clear advantage we observed after 2 u compared with 5 u was a marked decrease in the frequency of nausea and the need for antiemetic therapy (5% vs 32.5%). This may reflect the degree of sudden haemodynamic change, as the incidence of nausea is correlated to the degree of hypotension at Caesarean section.<sup>12</sup> If this finding is confirmed in subsequent studies, this benefit on its own is enough to recommend the use of 2 u in preference to 5 u for elective Caesarean section.

Although decreasing (or omitting) the oxytocin bolus minimizes haemodynamic changes,<sup>1,2</sup> many doctors may be cautious about doing so because of concerns about poor uterine contraction and resultant increased bleeding.<sup>8</sup> The assessment of uterotonic efficacy at Caesarean section has been attempted by estimation of blood loss, the measurement of postoperative haemoglobin, assessment of uterine tone, and requests for supplementary uterotonic drugs. The last two measures, though subjective, appear to be more sensitive, and less likely to be confounded by other causes of obstetric bleeding. For instance, two studies comparing different oxytocic regimens at Caesarean section, with 694 and 321 patients, reported differences in uterine tone and the need for further uterotronics, but were unable to detect differences in blood loss or change in haemoglobin.<sup>3,13</sup>

We found no differences between the groups in blood loss, uterine tone, or the need for further uterotronics. However, we did find a tendency for the initial uterotonic effect to 'wear off' in both groups, as the need for further uterotonic drugs increased from 6.25% of patients at 5 min to 17.5% by 20 min. This is in accordance with oxytocin's short half-life of 10–15 min,<sup>14</sup> but also implies that the initial infusion rate of 10 u h<sup>-1</sup> may be insufficient. Our results therefore do not agree with those of Carvalho and

colleagues,<sup>7</sup> who in a dose-finding study of 40 patients estimated the ED90 of oxytocin at elective Caesarean section to be only 0.35 u, and found no need for further oxytocin with a maintenance infusion of 2.4 u h<sup>-1</sup>. Although the reasons for the disparity are unclear, it appears that unlike our study, they did not re-assess uterine tone after an initial response was achieved.<sup>7</sup>

As an alternative to an oxytocin bolus plus infusion, the long-acting oxytocin analogue carbetocin has potential benefits in terms of convenience and a decreased need for further uterotronics.<sup>15</sup> In a large Caesarean section study, a 100 µg bolus of i.v. carbetocin was compared with a 5 u oxytocin bolus followed by a 2.5 u h<sup>-1</sup> infusion.<sup>13</sup> Carbetocin resulted in fewer requests for additional uterotronics (4.7% compared with 10.1%), with a comparable incidence of nausea but a greater decrease in arterial pressure.<sup>13</sup> Consistent with our data, the median time for requiring additional uterotonic therapy in the oxytocin bolus plus infusion group was 11 min.<sup>13</sup> Further research is needed to determine whether a smaller oxytocin bolus dose and a faster infusion rate would result in a more favourable balance of efficacy and side-effects.

An important limitation of our study is that we only studied elective patients at low risk of postoperative bleeding. The situation at emergency Caesarean section is quite different: as uterine responsiveness may be greatly decreased in this situation, higher doses of oxytocin are often required, and the early use of alternative uterotronics (e.g. ergometrine) may be preferable.<sup>3,16</sup>

In conclusion, we found that at elective Caesarean section, 2 u of i.v. oxytocin results in less haemodynamic change than 5 u, with less nausea and no difference in the need for additional uterotonic drugs.

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