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EDITORIAL

Oxytocin protocols during cesarean delivery: time to acknowledge the risk/benefit ratio?

A hormone discovered and synthesized over 50 years ago, oxytocin is currently used in the majority of births in developed countries and a growing number of births in the developing world.[1] Commonly employed to induce or augment the process of labor to effect vaginal delivery, oxytocin is also used as the first line drug to restore uterine tone and minimize postpartum blood loss following cesarean delivery. The purpose of this editorial, which is echoed in the review article by Dyer and colleagues in this issue of IJOA,[2] is to illuminate the risks associated with large intravenous (i.v.) bolus doses of oxytocin administered during cesarean delivery and to advocate an evidenced-based, infusion approach to dosing.

The administration of oxytocin is associated with significant maternal, fetal, and neonatal adverse events. Maternal arrhythmias, hypotension, uterine hyperstimulation and hyponatremia,[3,4] fetal decreases in oxygen saturation (SaO_2) related to contraction frequency,[5,6] and neonatal seizures, hyperbilirubinemia, or retinal hemorrhage[7,8] have been reported following oxytocin use. During cesarean delivery, with oxytocin administered following delivery, maternal morbidity and mortality are the most relevant concerns. The 1997–99 triennial audit of the Confidential Enquiries into Maternal Deaths in the United Kingdom (UK), reported the deaths of two women from cardiovascular instability following an i.v. bolus of oxytocin 10 IU.[9] Awareness of these deaths resulted in a dose reduction in the UK to an i.v. bolus of 5 IU;[2] however, even this dose, and the method of administration, may cause hypotension, tachycardia, decreased free water clearance, peripheral flushing, nausea, emesis and signs of myocardial ischemia.[10–13]

Although practitioners may be aware of these risks, the associated professional liability is the proverbial mountain hidden in plain sight: oxytocin remains *the* drug most commonly associated with preventable adverse events during childbirth, and *the* drug implicated in nearly half of all paid obstetric litigation claims.[14] Moreover, the United States Food and Drug Administration (FDA) has placed a black box warning restricting oxytocin use (during labor) to *medical* indications.[15] Furthermore, the Institute for Safe Medication Practices (ISMP), an independent, nonprofit organization whose recommendations are utilized by groups including the Joint Commission in evaluating medication safety, recently added oxytocin to the list of *high-alert* medications.[16] This distinction, which identifies drugs "bearing a heightened risk of harm when used in error" that may "require special safeguards to reduce the risk of error", has been applied to only 11 other specific drugs.[16]

In an effort to improve patient safety, the *cause célèbre* of the contemporary medical community, practitioners have questioned the high-dose, non-standardized oxytocin practices currently in use.[17–19] The re-evaluation of oxytocin acknowledges the unpredictable therapeutic index (in which a given dose can result in either hypertonic contractions or no discernable effect), use of excessive starting doses, lack of a predetermined, lock-step protocol that predicates increasing doses on determination of insufficient lower doses, and practices that contribute to normalization of deviance (degradation of professional or technical standards based on individual experience).[17–19] Interestingly, this call to action stops abruptly at the door of the operating room, despite literature demonstrating that common clinical practices result in unnecessary, excessive oxytocin doses. In non-laboring women undergoing cesarean delivery, a 'ceiling effect' of oxytocin 5 IU is witnessed, beyond which no further improvement in uterine tone and blood loss is observed;[20] in laboring women, high doses of oxytocin did not obviate the need for additional uterotonic agents.[12] Interestingly, a small loading dose of oxytocin (ED 90 = 0.35 IU) has been determined to be sufficient in producing adequate uterine contractions during elective cesarean deliveries in non-laboring women;[22] a similarly low loading dose (ED 90 = 2.99 IU) is required in laboring women.[23] Women who have received oxytocin augmentation for labor have greater blood loss despite higher oxytocin doses; this appears to originate from signal attenuation and desensitization of the oxytocin receptors, in a time and concentration dependent manner.[24–27] Similarly, continued high-dose oxytocin exposure in the postpartum period may also lead to acute receptor desensitization and render the myometrium less responsive to additional oxytocin.[27]

The current guidelines for the administration of oxytocin during cesarean delivery are diverse, empiric, and vague. The most recent editions of major obstetric

Table 1 Oxytocin protocol for cesarean delivery: "Rule of threes"

3 IU oxytocin intravenous loading dose* (administered no faster than 15 seconds[12])
3 min assessment intervals. If inadequate uterine tone, give 3-IU oxytocin intravenous rescue dose.
3 total doses of oxytocin (Initial Load + 2 Rescue Doses)
3 IU oxytocin intravenous maintenance dose (3 IU/L at 100 mL/h)
3 Pharmacologic options (e.g. ergonovine, carboprost and misoprostol) if inadequate uterine tone persists

* An initial dose of 3 IU oxytocin is sufficient for effective uterine contractions for both non-laboring[12,21] and laboring[23] women. Preferably this dose should be administered in the form of a rapid infusion, rather than a bolus. Maintenance oxytocin infusion can be administered for up to 8 h following delivery.

texts,[28–30] either avoid mentioning an oxytocin dose during cesarean delivery or provide a range of 20-40 IU. The British National Formulary (BNF), the American College of Obstetricians and Gynecologists (ACOG), and the Society of Obstetricians and Gynaecologists of Canada (SOGC) provide guidance for cesarean deliveries accompanied with a postpartum hemorrhage (PPH), indicating that a range from 5 IU to 40 IU can be used; further, the SOGC suggests that oxytocin 10 IU can be given as an i.v. push.

A stepwise, standardized, check-list driven algorithm for oxytocin use during cesarean delivery is needed to guide practitioners in a clear and concise manner. This algorithm should encompass laboring and non-laboring women, as well as prophylactic and therapeutic uses of oxytocin. More specifically, we believe that the following points should be incorporated into a protocol: (1) oxytocin should be used in initial doses of less than 5 IU; (2) oxytocin should not be administered as a rapid i.v. bolus; (3) an initial rapid infusion of oxytocin should be followed by a maintenance infusion; (4) higher initial and infusion doses of oxytocin offer no clinical benefit and should be avoided; and (5) if it appears that oxytocin is not producing effective uterine contractions, other uterotonic drugs acting via different pathways should be considered. We are currently validating a reasonable ''Rule of Threes'' protocol which incorporates these tenets, is evidence-based, and easy to remember (Table 1). In the application of any protocol, a multidisciplinary, team approach is necessary to assess its impact and make improvements.

The synthesis and use of oxytocin represents an important advance to modern obstetric care; however, the significant risk with minimal benefit associated with excessive doses of oxytocin, particularly when given as an i.v. bolus, deserves a robust evaluation. An evidence-based oxytocin protocol that uses low doses given judiciously, incorporates a timed process of uterine assessment, and utilizes alternative uterotonic agents in a more timely manner should improve the quality of care, reduce complications, and enhance the satisfaction and safety for patients undergoing cesarean delivery. Further investigation into appropriate oxytocin protocols, coupled with the re-evaluation of such protocols for labor initiation and augmentation, should make the drug's next golden anniversary a real cause for celebration.

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