What Do Current Information and Evidence Suggest to Us for Oxytocin Use During Caesarean Section?

Berrin Günaydın¹, Ayça Taş Tuna²

¹Department of Anaesthesiology and Reanimation, Gazi University Faculty of Medicine, Ankara, Turkey

²Department of Anaesthesiology and Reanimation, Sakarya University Faculty of Medicine, Sakarya, Turkey

Oxytocin is the first-line agent in the prevention and treatment of uterine atony and maintenance of uterine tone. Since there are several different practices related to the use of oxytocin during caesarean sections, we would like to address the latest information and evidence for rational oxytocin use.

Keywords: Oxytocin, caesarean section, current information

Ever since the presentation titled 'Uterotonics' was included in the scientific program of the 45th Turkish Anaesthesiology and Reanimation Congress within the scope of the development course in 2011, knowledge based on evidence regarding the use of oxytocin is continuously shared in almost all the obstetric anaesthesia panels of congresses organized by both the Turkish Anaesthesiology and Reanimation Society and the Regional Anaesthesia Society (1, 2). However, in this year's 48th Turkish Anaesthesiology and Reanimation Congress, we noticed from the questions that were asked at the end of the panel entitled 'Neuraxial Blockade in Caesarean Section and Controversial Topics', which also included a talk titled 'Uterotonics', that most of this current knowledge has not been properly understood (3). Therefore, we wanted to clarify and point out the evidence-based findings once again in this issue of our journal, which is the main publishing source of the Turkish Anaesthesiology and Reanimation Society.

Endogenous oxytocin is a polypeptide of nine amino acids produced in the posterior pituitary gland. Oxytocin, which was discovered by Sir Henry Dale, was first synthetically synthesized by Du Vigneaud in 1953. Oxytocin is the first choice in the prevention and treatment of uterine atony and in the maintenance of tonus. Ergot derivatives and prostaglandins (E1, F2 α and E2) are the second and third choices, respectively.

The mechanism of action of oxytocin is mediated to G-proteins on the uterus myocyte surface and by producing phospholipase-C-mediated 1,2 diacylglycerol and 1,4,5 inositol triphosphate and by binding with calmodulin with the increased intracellular calcium and activation of the myosin light-chain kinase that is responsible for uterine smooth muscle contraction (4).

Following two maternal mortalities that were reported in England between 1997 and 1999 after 10 IU intravenous (IV) bolus doses of oxytocin, the IV bolus dose of oxytocin was decided to be lowered to 5 IU. However, even after halving this dose, signs of hypotension, tachycardia, decrease in free water clearance, peripheral flushing, nausea-vomiting and myocardial ischemia were observed (5-8).

The United States of America Food and Drug Administration placed a 'black box' warning on oxytocin and pointed out the specific dosage form, while the Institute for Safe Medical Practice added oxytocin to the list of 'high alert medicine' (9, 10).

To establish a sufficient uterine tonus, oxytocin can be administered by bolus or infusion. It was reported that in 1997, the ceiling effect was observed with 5 IU oxytocin in elective caesarean sections (non-labouring women). Later research revealed that the IV bolus loading dose for elective caesarean sections in the pregnant not active was ED90=0.35, while in the labouring pregnant, this dose was relatively higher (ED90=2.99) (12, 13). Based on this, it became clear that a protocol was needed

Table 1. Oxytocin administration protocol according to the Rule of Threes

3 IU IV loading dose (not to be given faster than 15 s)
Evaluate every 3 min; if insufficient, 3 more IU IV to be given
Oxytocin is given 3 times (starting loading dose+twice more)
3 IU oxytocin maintenance doses (3 IU L ⁻¹ at a rate of 100 mL h ⁻¹)
If the uterine tonus is still insufficient, other pharmacological options are considered (for instance, ergonovine, carboprost, misoprostol)
IU: international unit; IV: intravenous

regarding the doses of both prophylactic and therapeutic oxytocin, in both labouring and non-labouring women. Therefore, an evidence-based and easy-to-remember protocol for caesarean sections titled 'Rule of Threes' was published by Tsen and Balki (Table 1) (14).

According to this protocol, the following points are to be considered when administering oxytocin:

- Starting dose to be <5 IU
- Avoid rapid IV bolus
- Start rapid infusion+slow maintenance infusion
- Infusing it with normal saline or lactated Ringer's solution
- Avoid infusing it with hypotonic fluid in case it results in dilutional hyponatremia
- If effective uterus contractions are still not present, other uterotonics that are effective must be considered (14).

For uterine atony leading to postpartum haemorrhage, the Royal College of Obstetricians and Gynaecologists, recommends oxytocin 40 IU in a 500 mL crystalloid solution to be administered at 125 mL h⁻¹ rate (15).

Even though the *in vivo* half-life of oxytocin that is broken down in the plasma by oxytocinase is as short as 10–15 min, several maternal, foetal and neonatal adverse effects are observed upon administering oxytocin in caesarean sections (Table 2) (16). Hypotension and tachycardia, the most commonly observed cardiovascular side effects in mothers, are dose-dependent. Coronary vasoconstriction and myocardial ischaemia manifest themselves by a change in the ST segment. In elective caesarean sections performed under spinal anaesthesia, ST depression was observed with 10 IU IV bolus oxytocin, through vectorcardiography/Holter monitoring (17, 18).

Oxytocin receptor desensitization in the uterine muscle is reported in *in vitro* and *in vivo* studies on oxytocin. It was observed that haemorrhage due to atony continued or increased, even though high-dose oxytocin was used for labour

Table 2. Adverse effects of oxytocin

Maternal	Foetal
Arrhythmia	Decrease in SaO ₂ dependent on contraction frequency
Hypotension	Neonatal
Tachycardia	Seizure
Myocardial ischaemia	Hyperbilirubinaemia
Nausea-vomiting	Retinal haemorrhage
Headache	
Uterine hyperstimulation	
In high doses, albeit rarely, water retention, hyponatremia, seizure and coma because of the structural similarity of oxytocin to vasopressin.	

induction. This situation is caused by the development of time- and concentration-dependent desensitization in oxytocin receptors and by postpartum high-dose oxytocin rendering the uterine muscle unresponsive to oxytocin, again due to acute receptor desensitization (19, 20).

In medicine, an effective implementation of any protocol can only be achieved through a multidisciplinary approach. Therefore, we, as anaesthesiologists, can raise awareness by knowing current evidence and by sharing these evidences widely. Furthermore, we believe that drawing attention is required in order to provide rational oxytocin use for caesareans throughout the country with the cooperation of the Turkish Society of Obstetrics and Gynaecology.

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