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REVIEW ARTICLE

Oxytocin in cesarean-sections. What's new?

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Abstract Oxytocin is the uterotonic agent of choice in the prevention and treatment of postpartum uterine atony. Nevertheless, there is no consensus on the optimal dose and rate for use in cesarean sections. The use of high *bolus* doses (e.g., 10 IU of oxytocin) can determine deleterious cardiovascular changes for the patient, especially in situations of hypovolemia or low cardiac reserve. Furthermore, high doses of oxytocin for prolonged periods may lead to desensitization of oxytocin receptors in myometrium, resulting in clinical inefficiency.

PALAVRAS-CHAVE
Ocitocina;
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Dose

Ocitocina em cesarianas. O que há de novo?

Resumo A ocitocina é o uterotônico de primeira escolha na prevenção e no tratamento da atonia uterina após o parto. Apesar disso, não existe consenso sobre qual a dose e velocidade ideais de seu uso em cesarianas. O uso de altas doses (por exemplo, 10 UI de ocitocina) em bolus pode determinar alterações cardiocirculatórias deletérias para a paciente, especialmente em situações de hipovolemia ou baixa reserva cardíaca. Além disso, altas doses de ocitocina por períodos prolongados podem levar à dessensibilização dos receptores de ocitocina localizados no miométrio e resultar em ineficácia clínica.

Introduction

Oxytocin, the first polypeptide hormone to be synthesized in 1953 by Vincent Du Vigneau, is the drug of choice for both prevention and treatment of uterine atony after childbirth.[1] Oxytocin binds to its receptor on the surface

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of the myometrium cell, interacts with phospholipase C, and generates diacylglycerol and inositol triphosphate. Diacylglycerol leads to the synthesis of prostaglandins, important in the mechanism of contraction, while inositol triphosphate increases calcium concentration in the cell sarcoplasmic reticulum, thereby determining the contraction of myometrium.

Uterine atony is the leading cause of postpartum bleeding, which gives oxytocin an important role in reducing the severity of uterine bleeding and hence maternal mortality. According to the website of the Ministry of Health, a clear decrease (69.3%) in the risk of maternal death from hemorrhage occurred in Brazil between 1990 and 2010.[2] The best training of professionals involved in the care of these women, as well as the rational use of available drugs to prevent or treat uterine atony (such as oxytocin, for example) may be one of the factors responsible for this reduction.

The aim of this review was to update the article on the use of oxytocin in cesarean sections published by these authors seven years ago.[3] A literature search in PubMed database was performed with the keywords ''oxytocin'' and ''cesarean section'' up to April 2013, with preference to articles published from 2007 (year of the previous review publication). The authors selected the items considered most relevant to the practice of anesthesiologists, besides obtaining possible references from the articles initially selected.

Use in cesarean sections

Despite being a fairly common practice, oxytocin is used in cesarean sections empirically. Surprisingly, to date there is no consensus about the ideal regime of its administration, even after 60 years of its synthesis and routine use in obstetric centers. An example is the study by Wedisinghe et al.,[4] in which they reported the existence of at least 38 different regimens of oxytocin infusion in the UK. Although there is no such documentation, this fact does not seem to be very different from what happens in Brazilian medical institutions.

The variability of doses and infusion rates of oxytocin complicates a meta-analysis that contribute to the establishment of a consensus on the best use of oxytocin to prevent postpartum bleeding.[5] Anyway, it must be remembered that oxytocin is used prophylactically in most obstetric patients as supplementation of endogenous oxytocin. Thus, the use of high doses (either by bolus or continuous infusion) would be unnecessary and even detrimental to patients due to the possibility of side-effects (particularly cardiovascular).

Butwick et al.[6] attempted to find the minimum effective dose (ED) of oxytocin that would determine a satisfactory uterine contractility during elective cesarean section. To this end, 75 pregnant women primigravidae and without risk factors for developing uterine atony were evaluated with logistic regression method. The authors concluded that satisfactory uterine contractility could be obtained with the use of low-dose oxytocin bolus (0.5–3 IU). The calculation of ED to promote uterine contraction in 50% (ED_{50}) and 90% (ED_{90}) of patients was possible because, curiously, the uterine tone was evaluated as satisfactory in 73% of cases by the obstetric team in placebo group (without oxytocin). It is possible that this fact has occurred due to the uterine massage performed by the obstetrician for the uterus externalization. However, the isolated uterine massage does not spare the use of oxytocin because the placebo group required rescue oxytocin. This confirms that the optimum approach is the combination of prophylactic oxytocin and uterine massage.

Oxytocin administration by continuous infusion in cesarean section reduces the need for using other uterotonic agents. Sheehan et al.[7] performed a prospective, randomized, multicenter study in Ireland with 2069 women who underwent elective cesarean section. All patients received oxytocin 5 IU in one minute, followed by oxytocin 40 IU diluted in 500 mL saline for four hours or saline alone (placebo group). Although the infusion of oxytocin have not affected the general occurrence of obstetrical bleeding, there was a significant reduction in the need for other uterotonic agents with the use of bolus followed by infusion of oxytocin compared with the use of oxytocin bolus alone (12.2% vs. 18.4%; $p < 0.001$).

Thus, the use of low-dose oxytocin bolus does not spare the use of continuous infusion of oxytocin. Although there is no record on that probably the use of oxytocin continuous infusion alone (diluted in saline and controlled by drip), that is, without initial bolus, is the approach most commonly used by Brazilian anesthesiologists. George et al.[8] studied 50 patients undergoing elective cesarean section without risk factors for uterine atony. The authors showed that oxytocin ED_{90} in these patients was 0.29 IU min^{-1}, which is equivalent to diluting 15 IU of oxytocin in 1 L saline and infuse this solution in 1 h. These results correspond to 50% less than the previously used infusion at the institution where the study was conducted. However, due to the large variation of the confidence interval (95% CI, 0.15–0.43 IU min^{-1}), this ED_{90} estimate may be inaccurate. Thus, other studies are needed to confirm these results.

King et al.[9] unlike the previously mentioned authors, evaluated patients who had at least one risk factor for the development of uterine atony (uterine distention, prolonged exposure to oxytocin prior to cesarean section, chorioamnionitis, and others). The use of initial bolus of oxytocin (5 IU), followed by oxytocin infusion (40 IU in 500 mL saline infused over 30 min, followed by 20 IU in 1 L over 8 h) did not alter the need for other uterotonic agent in the first 24 h after cesarean section, when compared with infusion alone.

With the risks and benefits of using oxytocin as a base, Tsen and Balki[10] proposed a management regime based on evidence and called ''rule of threes''. The authors suggest the use of 3 IU of intravenous oxytocin (administered at higher speed than 15 s) as the starting dose, which may be repeated two more times (in three minute intervals) if uterine tone is not satisfactory. The oxytocin maintenance dose is 3 IU L^{-1} at 100 mL h^{-1}.

Extrauterine actions

Much more complex than previously thought, the extrauterin actions of oxytocin go beyond the cardiovascular system.