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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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Dessensibilização;
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.

For example, oxytocin may increase maternal temperature with deleterious consequences for both mother and fetus by the increased secretion stimulation of inflammatory mediators (PGE and PGF2α). However, in a retrospective study of pregnant women with intrauterine fetal death in the second trimester of pregnancy, the use of high-dose oxytocin (0.267–1.667 IU min^{-1}) did not determine rise in maternal temperature.[11]

Hemodynamic changes that occur during cesarean section have multifactorial causes, such as sympathetic nervous system blockade secondary to the spinal anesthesia, aortocaval decompression and maternal autotransfusion after placental delivery, bleeding, use of vasopressor, etc. The use of oxytocin is just one of these causes and is directly dependent on the way it is administered (dose and infusion rate).

Human vascular endothelial cell has oxytocin receptors that are structurally identical to receptors present in myometrium and mammary gland.[12] The interaction of oxytocin with its endothelial receptor determines calcium-dependent response via nitric oxide, resulting in smooth muscle relaxation of resistance and capacitance vessels. Thus, vasodilation is the primary cardiocirculatory event after the use of oxytocin. Tachycardia, increased stroke volume and cardiac output (CO) occur as compensatory mechanisms to vasodilation. These effects are more pronounced when oxytocin is administrated as bolus and can be harmful to patients with impaired cardiovascular reserve.

The use of high-dose bolus (e.g., 5–10 IU of oxytocin) has frequently been discouraged, particularly after reports of maternal death after bolus administration of oxytocin (10 UI) to hypovolemic patient due to uterine atony, according to the triennial survey of maternal death occurred in the UK.[13]

In elective cesarean sections, standard non-invasive monitoring (ECG, noninvasive blood pressure, and pulse oximetry) is used, which may not detect the possible hemodynamic changes determined after the use of oxytocin, especially because they are most pronounced about the first minute after oxytocin administration. While not routine during cesarean section, invasive monitoring methods have allowed a better understanding of the hemodynamic profile of these patients after oxytocin administration. Langesaeter et al.[14] with invasive monitoring (LiDCOPlus® monitor) in healthy pregnant women, observed an increase in cardiac index (CI), decreased systemic vascular resistance (SVR) and systolic blood pressure (BP) (range of 36–62 mmHg) 45 s after oxytocin injection. This same group of authors studied 18 patients with preeclampsia who underwent cesarean section.[15] With the same monitoring as the previous study (LiDCOPlus®) connected to the radial artery of patients, the authors found increased heart rate (HR) and decreased SVR and BP in all patients receiving oxytocin (5 IU) after delivery. The hemodynamic instability that can occur during postpartum hemorrhage may not be solely due to hypovolemia, but the association of both hypovolemia and use of oxytocin bolus.[16]

Hemodynamic changes determined by oxytocin are directly dependent on dose and rate of infusion. Thomas et al.[17] found that bolus administration of oxytocin (5 IU over 5 s) promotes greater decrease in mean BP and greater increase in heart rate than the administration of oxytocin (5 IU over 5 min) in patients undergoing elective cesarean section. The authors recommend that oxytocin should be administered slowly to minimize cardiovascular effects that may not be well tolerated by the hypovolemic patient or with low cardiac reserve.

The administration of oxytocin (5 IU over 3 min) as a loading dose, followed by oxytocin infusion (30 IU over 4 h) did not determine significant hemodynamic changes compared to administration of the same loading dose, followed by placebo infusion (crystalloid solution).[18] With the thoracic bioimpedance method, the studied parameters (CI, left ventricular work and SVR) were gradually returning to preoperative values of these patients during the 4 h of oxytocin infusion, probably due to spinal block regression.

ECG changes suggestive of myocardial ischemia have been reported after administration of oxytocin bolus (10 IU over 30 s) after clamping the umbilical cord during elective cesarean sections.[19] These changes were accompanied by hypotension, tachycardia, and breast discomfort, but were reversible and of short duration. However, the combination of hypotension, tachycardia, and coronary vasoconstriction may cause an imbalance between myocardial oxygen supply and demand and possible myocardial ischemia, even in patients without coronary disease.

With standard monitoring, changes in the patient's HR correlate better with changes in CO compared to variations in pressure values. Sartain et al.[20] demonstrated a greater increase in HR using oxytocin 5 IU compared to oxytocin 2 IU (32 ± 17 bpm vs 24 ± 13 bpm, respectively, $p = 0.015$). These doses were diluted to a final volume of 5 mL and infused over 5–10 s. All patients received oxytocin infusion (10 IU h^{-1} over 4 h) after loading dose.

In this context of hemodynamic changes associated with oxytocin, Dyer et al.[21] performed an important study comparing maternal hemodynamic effects after the use of phenylephrine or ephedrine for arterial hypotension management after spinal anesthesia in cesarean sections. Twenty patients who received no vasopressors (ephedrine) were randomized to receive oxytocin 2.5 IU or oxytocin 2.5 IU associated with phenylephrine (80 μg) 30 s after birth. The authors concluded that phenylephrine alleviates maternal hemodynamic effects of oxytocin. Thus, in clinical practice, we often end up managing possible hemodynamic effects of oxytocin when a direct action vasopressor (phenylephrine or metaraminol) is used in the treatment of maternal hypotension secondary to sympathetic blockade in spinal anesthesia.

As can be seen, the hemodynamic changes that could be caused or contributed by oxytocin have been one of the major concerns for researchers today. The clinical significance of these findings still seems unclear, as the effects were transient and reversible in most cases. Oxytocin, probably determine more significant hemodynamic changes in patients who had low heart reserve or hypovolemia; therefore, the use of oxytocin bolus in this particular group of patients should be avoided.[22]

According to the National Health Surveillance Agency (Anvisa),[23] currently oxytocin can be found in Brazil for hospital use under the following names: Syntocinon®, Oxiton®,

Table 1 What should I learn from this review.

Oxytocin is the uterotonic of choice for the prevention and treatment of uterine atony
There is no consensus on the optimum dose and rate of its administration in cesarean sections
Drip infusion of oxytocin (5–20 IU) diluted in crystalloid solution seems to be the usual mode of use in cesarean sections in Brazil
The use of oxytocin bolus (e.g., 10 IU) should be avoided, particularly in hypovolemic patients or those with low cardiovascular reserve
High doses of or prolonged exposure to oxytocin can lead to desensitization of its receptors and be translated clinically as therapeutic inefficacy
In case of response failure after the use of oxytocin, consider other uterotonic agents (ergot derivatives, prostaglandins)
Carbetocin is a synthetic analog of oxytocin, but with a half-life four times longer, and no therapeutic dose established yet

Naox®, Obstecina®, Ocitoc®; all with chlorobutanol added as a preservative in the composition. In vitro study with human atrial myocytes showed that chlorobutanol has negative inotropic action.[24]

Desensitization of oxytocin receptors

In 2004, Carvalho et al.[25] demonstrated that oxytocin ED_{90}—the effective to promote satisfactory uterine contractions in 90% of patients—would be around 0.35 IU. The study was performed with patients scheduled for elective cesarean section without risk factors for uterine atony, with the logistic regression method. Based on experimental works of female rat myometrium, the same group conducted a study with similar design, but now involving pregnant women who underwent cesarean section due to dystocia and who received oxytocin during labor. In such cases, it was found an increase in oxytocin ED_{90} of almost ninefold (2.9 IU).[26] The likely explanation for these results would be the occurrence of desensitization of oxytocin receptors in myometrium after prolonged exposure to oxytocin during labor.

Continuing these investigations, Balki et al.[27] studied myometrium fragments of pregnant mice and found a decrease in the amplitude of myometrial contractions when these fragments were previously exposed to oxytocin compared to control group (saline). Although the contractility caused by oxytocin was higher than the contractility caused by ergonovine or PGF2, the uterotonic effect of these drugs was not affected by prior exposure to oxytocin. This study supports the concept of desensitization of myometrial receptors after prolonged exposure to oxytocin. Clinically, these results demonstrate that high doses of oxytocin for prolonged periods can lead to a lower efficiency of uterotonic action or even uterine atony.

Measurement of oxytocin in blood

There are few studies describing oxytocin levels in blood. Usually these papers involve pregnant women in labor, or are experimental animal studies, with radioimmunoassay (RIA) for oxytocin measurement.

Serum levels of oxytocin by enzyme immunoassay technique (ELISA) have been studied in pregnant women undergoing elective cesarean section.[28] Although this study was not designed to correlate serum doses of oxytocin with clinical efficacy, the authors demonstrated that the use of Oxytocin 80 IU (2.67 IU min^{-1}) determined serum levels of oxytocin larger at 5 and 30 min, compared with the use of 10 IU (0.33 IU min^{-1} or 2.67 IU min^{-1}). The technique used (ELISA) had the advantage of handling non-radioactive material, compared with the RIA technique. Furthermore, the management of peptides, such as oxytocin, requires special care because storage of samples should be at −70 °C to prevent oxytocin degradation by maternal aminopeptidases.

Additional studies should be developed in an attempt to correlate oxytocin blood measurement with satisfactory uterine contractility and lower incidence of side effects. Apparently, the clinical efficacy of oxytocin is more dependent on its interaction with its receptor than actually with its blood concentration.

Carbetocin

Carbetocin, a synthetic analog of oxytocin, has the same affinity as oxytocin for myometrial receptors, but differs for having a much longer plasma half-life than oxytocin (40 min vs. 15 min, respectively), which has aroused special interest as an option to the use of oxytocin to prevent uterine atony.[29]

Cordovani et al.[30] used carbetocin at doses of 80 μg and 120 μg in patients with low risk of postpartum bleeding and who underwent elective cesarean section. In these patients, the uterine tone was satisfactory in 87% of cases; there was no significant difference between the doses used. The authors reported a high incidence (55%) of hypotension with these doses, since carbetocin has a hemodynamic profile similar to that of oxytocin. Moertl et al.[31] in a prospective randomized study of 56 women undergoing elective cesarean section, compared bolus doses (10 s) of carbetocin (100 μg) with oxytocin (5 IU). There was an increase in HR (14.20 ± 2.45 bpm vs. 17.98 ± 2.53 bpm, respectively) and decrease in BP in both groups, especially after 30–40 s of administration of each of these uterotonic drugs. These results are comparable to those found by Rosseland et al.,[32] who used the same doses (5 IU of oxytocin and 100 μg of carbetocin, in addition to a placebo group) in a similar group of patients, but invasively monitored with radial artery catheterization. In Brazil, carbetocin is registered

with Anvisa under the trade name Duratocin® in 1 mL vials (100 μg mL^{-1}).[23] However, other studies should be developed to establish the effective dose of carbetocin and if its use reduces the postpartum incidence of bleeding or the need for blood transfusion.

Finally, the essential points of this review may be seen in Table 1.

Conflicts of interest

The authors declare no conflicts of interest

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