Β5. ΘΕΜΑΤΑ ΜΑΙΕΥΤΙΚΗΣ ΑΝΑΙΣΘΗΣΙΑΣ

Β5.Α. UTEROTONIC AND VASOACTIVE DRUGS IN OBSTETRIC ANESTHESIA

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Anesthesiologists involved in obstetric anesthesia use uterotonic and vasoconstrictor drugs in their everyday practice to prevent or treat uterine atony and postpartum hemorrhage as well as hypotension after neuraxial anesthesia respectively. Considerable past and current research has shown that these agents have a narrow therapeutic range. Surprisingly enough current guidelines for the administration of these drugs during cesarean delivery are diverse, empiric, and vague. A detailed knowledge by anesthetists of optimal drug use, dosage and side effects is therefore required.

The most common cause of postpartum hemorrhage is uterine atony which complicates 1 in 40 births in the united states and is responsible for at least 75% of cases of postpartum hemorrhage[1,2]. After placental delivery the uterus contracts and stays contracted so its myometrial fibers occlude spiral arterioles. Oxytocin is the only evidence based uterotonic drug given for prophylaxis and therapy of uterine atony[3,4]. Carbetocin is a synthetic analogue of oxytocin with different pharmacological profile, and more expensive. Second line uterotonics include ergot alkaloids, such as methylergonovine and ergometrine, and synthetic analogues of prostaglandins F2α (carboprost), E1 (misoprostol) and E2 (dinoprostone). Syntometrine is a combination preparation, seldom used during cesarean section, containing 5 iu oxytocin and 0,5 mg ergometrine. Manual uterine massage and oxytocin are almost universally accepted as the first line treatments of choice for uterine atony. Methylergonovine and carboprost are second line agents in most treatment protocols[5,6]. The choice of which therapeutic agent to use should be based on the comorbidities of the patient, the clinical judgement of the practitioners involved in the case, and of course availability of drugs[7,8].

Oxytocin is a short polypeptide causing a stimulatory effect on myometrial contractility by increasing the intracellular concentration of calcium. Oxytocin receptors appear in myometrial cells at approximately 13 weeks gestation and increase in concentration until term. Their distribution is not uniform throughout. During elective cesarean an oxytocin bolus is used to initiate adequate uterine tone, followed by an oxytocin infusion to maintain uterine contractility. Initial dose and infusion rate should optimize drug efficacy while minimizing side effects[9,10]. Repeated exposure of the myometrial cells to oxytocin leads to oxytocin receptor desensitization, so repeated doses of oxytocin may become increasingly ineffective[11,12,13] and second line uterotonics should be considered earlier for laboring patients. The recommended dose, timing and rate of administration for oxytocin during cesarean delivery remain ambiguous[14,15]. Adverse effects of the drug include hemodynamic instability, nausea, vomiting, headache, flushing and in high dosages

hyponatremia, seizures, and coma. The "Rule of Threes" algorithm can be used to minimize dose and rate related side effects by applying a standardized method of administering oxytocin during elective cesarean deliveries[16,17,18].

Carbetocin is a synthetic analogue of oxytocin with a half-life 4-10 times the duration of oxytocin. A tetanic uterine contraction is produced 2 min after an intravenous injection of 10-70 μg, which persist for approximately 11 min. There is still no clear-cut dosage recommendation while the side effect profile of carbetocin is similar to that of oxytocin[19]. There is comparative efficacy of carbetocin and conventional uterotonics agents while heat stable carbetocin is being investigated as a potential alternative to oxytocin [20,21].

Ergot, derived from a fungus, was the first effective oxytocic drug. Ergometrine also known as ergonovine, is a naturally occurring alkaloid while methylergometrine is a synthetic analogue of ergonovine. Ergonovine is a partial agonist of α-adrenergic, 5HT-1 and dopamine receptors while the mechanism of action on the uterus is unknown. It provides rapid and sustained contraction of pregnant and non-pregnant uterus and although it is appropriately banned from intrapartum use still remains a second line uterotonic[22,23]. Dosage guidelines vary from 0,2 to 1 mg within an hour. The drug should be given cautiously because it raises arterial and pulmonary pressure and has a high incidence of vomiting and nausea.

Prostaglandins are bioactive lipids derived from arachidonic acid. They are synthesized within human fetal membranes and decidua. They play a major role in both the initiation and maintenance of labor by enhancing contractions and ripening the cervix. Prostaglandins F2α and E are reported to increase in a time dependent manner during later gestations indicating that they are important in the labor process[24]. Both influence myometrial contractility. Clinically synthetic analogues of prostaglandins have been used for many years for termination, labor induction and treatment of postpartum hemorrhage. Carboprost is a synthetic analogue of prostaglandin F2α. It can be used intramuscularly, intramyometrially while there is limited experience with intravenous administration. Frequently reported side effects include nausea, vomiting and diarrhea while it can precipitate severe bronchospasm and hypoxemia. Misoprostol is synthetic analogue of prostaglandin E1, inexpensive and widely available. Clinically useful routes of administration include the following: oral, buccal, sublingual, vaginal and rectal, with different pharmacokinetic profiles. Side effects include shivering, hyperthermia, tremor, and convulsions. Misoprostol remains a treatment option for uterine atony, but its utility as an adjunct to the other uterotonic medication may be limited [25].

Neuraxial anesthesia is the technique of choice for cesarean delivery[26,27]. Hypotension is a very common consequence of the sympathetic vasomotor block caused mainly by spinal or combined spinal epidural anesthesia. Maternal symptoms such as nausea, vomiting and dyspnea frequently accompany severe hypotension, and adverse effects on the fetus, including depressed Apgar scores and umbilical acidosis, have been correlated with severity and duration of hypotension. Amongst several actions taken to prevent and treat hypotension, like administration of fluids, ondasetron, positioning, and leg compression[28], it is unacceptable to proceed with spinal anesthesia without the availability of a vasopressor and an anticholinergic agent [29].

Vasopressor drugs mediate their cardiovascular effects primarily through their actions on α1, β1 and β2 receptors. Ephedrine not only has mainly indirect adrenergic receptor activity but also exerts weak direct effects, which explains the comparatively slow onset and long duration of action. Ephedrine typically increases heart rate and contractility by cardiac β1 adrenergic receptor stimulation. Phenylephrine has a potent direct α1 effect, with virtually no β effect. When given at higher than required doses it may induce bradycardia. Noradrenaline is a potent α1 adrenergic agonist, with comparatively modest β agonist activity. It causes marked vasoconstriction with some direct inotropic effects and it may be a reasonable alternative to phenylephrine, but there are concerns about the use of such a potent agent in a non-intensive care unit environment[30,31]. Adrenaline has high affinity for α1, β1 and β2 receptors. β effects predominate at low doses while α1 effects are more significant at higher doses.

There are considerable differences in practice among countries regarding the choice and method of administration of vasopressors in obstetrics patients[32]. Ephedrine became the drug of choice in obstetric anesthesia following work in animals, however it is now acknowledged that ephedrine in higher doses worsen fetal acidosis[33,34] due to direct effect on fetal metabolism that negates any improvement in uterine blood flow produced by normalizing blood pressure[35,36]. Clinical work dating from the 2000s indicated that α adrenergic agonists are effective at reducing hypotension and are associated with less neonatal acidosis than ephedrine[37]. Surveys of clinical practice indicate that there has been a shift away from what was the almost universal vasopressor of choice. Further research and studies could contribute to better clinical practice.

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