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INTRAVENOUS DEXMEDETOMIDINE INFUSION: A NOVEL THERAPY TO PREVENT THE POST-PARTUM HAEMORRHAGE AFTER CAESAREAN DELIVERY. A SYSTEMATIC REVIEW

Obstetrics & Gynaecology

Dr Vishnu Datt	Professor and HOD, Department of Anaesthesiology and intensive care, SGT Medical college & Hospital, Budhera, Gurugram, NCR -Delhi-122505.
Dr Diksha Datt	MD student, Department of PSM, SGT Medical college & Hospital, Budhera, Gurugram, NCR -Delhi-122505.
Dr Priyanka Dahiya	MD student, Department of Anaesthesiology and intensive care, SGT Medical college & Hospital, Budhera, Gurugram, NCR -Delhi-122505.
Dr Priyanka Kaushik	MD student,Department of Anaesthesiology and intensive care, SGT Medical college & Hospital, Budhera, Gurugram, NCR -Delhi-122505.
Dr Samya Agarwal	(Intern) JNMC, Belgaum, Karnataka.
Dr Sakshi Dhingra	MD student, Department of Anaesthesiology and intensive care, SGT Medical college & Hospital, Budhera, Gurugram, NCR -Delhi-122505
Dr Manju Puri	Professor, Department of Obstetrics and Gynaecology, SGT Medical college & Hospital, Budhera, Gurugram, NCR -Delhi-122505
Dr Rashmi Ray	Professor, Department of Obstetrics and Gynaecology, SGT Medical college & Hospital, Budhera, Gurugram, NCR -Delhi-122505
Dr Palak	MD Student, Department of Anaesthesiology and intensive care, SGT Medical college & Hospital, Budhera, Gurugram, NCR -Delhi-122505

ABSTRACT

Postpartum haemorrhage (PPH) is a serious obstetric emergency and a principal cause of maternal morbidity and mortality worldwide. The Prompt recognition and management are essential to mitigate adverse outcomes and ensure maternal safety. Routinely, intravenous oxytocin (5-20 IU) is the pharmacotherapy of choice and is recommended for the prevention of PPH in both vaginal delivery and caesarean section. In addition, other uterotonics are recommended as injectable ergometrine/methylergometrine 200 µg, oral or rectal mesoprostol 400–600 µg, or carbetocin 100 µg IM/IV for the prevention of PPH. In settings where experienced midwives are not available to administer injectable uterotonics, oral misoprostol could be helpful for the prevention of PPH.[1] Some authors have also recommended uterine massage with hot sponges to gain the uterine tone, abdominal aortic compression, and uterine artery clamping/ suturing to control bleeding and prevention of PPH. The primarily use of dexmedetomidine in obstetrics is to provide sedation, analgesia, and reducing shivering, blood pressure lowering in PIH, heart rate control in AF and adjuvant with heavy bupivacaine in Spinal anaesthesia and even general anaesthesia and in reducing the postoperative nausea and vomiting during caesarean delivery. In addition, Dexmedetomidine may also possess uterotonic properties, aiding in controlling uterine bleeding and PPH. Additionally, it has been investigated for its potential in preventing postpartum depression (PPD). Some case reports have suggested that dexmedetomidine with uterotonic effect can help reducing PPH following delivery. Although further research is needed to recommend its regular intravenous infusion (0.5-1 mcg/kg/hr) before the induction of anaestesia for prevention of PPH. This systematic review would highlight the utility of dexmedetomidine in prevention of PPH along with safety profile in the foetus.

KEYWORDS

Apgar score, caesarean delivery, dexmedetomidine, general anaesthesia, PPH,uterotonic, spinal anaesthesia

INTRODUCTION

Postpartum hemorrhage (PPH) is excessive bleeding after delivery of the fetus, and defined as the blood loss of more than 500ml after a vaginal birth or more than 1000ml after a Caesarean section within the first 24 hours with signs of hypovolemia.[1,2,3,4,5] uncontrolled PPH can lead to severe anaemia and disseminated intravascular coagulopathy,

TRALI because of blood products use, emergency lifesaving hysterectomy, multisystem organ failure, and death. Therefore, PPH is a major contributor to maternal mortality globally, and accounts for 25-43% of maternal deaths in developing nations particularly following delayed decision making for hysterectomy.[5,6] Commonly uterotonic medications used to manage and prevent PPH include oxytocin, ergometrine, misoprostol, and carbetocin.[7] These agents are routinely administered during the third stage of labor after delivery of the baby but before delivery of the placenta to prevent excessive bleeding. Among these, oxytocin is the preferred drug due to its effectiveness and availability, but other options are available if oxytocin alone is ineffective. In addition, some authors have suggested the use of dexmedetomidine (0.5-1 mcg/kg/hr) before delivery in prevention of PPH.[8] It has been reported that the administration of dexmedetomidine during caesarean section under general anaesthesia enhances the anaesthetic effects, reduce the anaesthetic dose and help stabilize the haemodynamics and improves uterine tone without any adverse neonatal effects.[9] However, its role in prevention of PPH and fetus safety profile is still not fully established. Therefore, in this systematic review, we have searched the literature, whether regular use of intravenous infusion of dexmedetomidine well before the delivery of the baby is safe for the baby and effective in prevention of PPH.

METHOD:

We utilized PubMed, google with several search algorithms, including a combination of terms such as “dexmedetomidine”, uterotonic effect, PPH with dexmedetomidine, “intravenous infusion”, Apgar score “obstetrics”, “pregnancy”, “cesarean delivery”, “complications”, “adverse effects”, “postoperative nausea and vomiting”, “postoperative shivering”, “postpartum depression” and “post-traumatic stress disorder”. We selected the criterion with the goal of effectively summarizing the current literature on the use and effects of IV dexmedetomidine in obstetric anesthesia for prevention of PPH, and effects on the fetus (Apgar score). The search was focussed on case reports, and RCTs or observational studies etc.

DISCUSSION

PPH is a profound blood loss after normal or cesarean delivery of the baby, and is a leading cause of maternal death worldwide along with hypertensive disorders of pregnancy, such as pre-eclampsia and eclampsia, and infections.[10] Approximately 14 million women experience PPH each year, resulting in around 70,000 maternal deaths. PPH is typically defined as lose of 500ml or more of blood after a vaginal delivery or 1000 ml or more after a cesarean section within the first 24 hours, with signs of hypovolemia like a 10% or greater drop in

hematocrit or changes in vital signs. [2,3,4,11,12,13,14] The causes are usually summarized by the 4 "T's" i.e. tone, trauma, tissue, thrombin.[15]

Risk factors for PPH includes; advanced aged mothers, multiple pregnancy, fetal macrosomia, prim-gravidity, grand multi-parity, preterm births, genital tract injuries, non-use of oxytocic's for PPH prophylaxis, and prolonged labor, anemia, obesity, and absence of antenatal care (ANC) visits, labor induction, cesarean birth and intra-uterine fetal deaths, general anaesthesia,and use of inhalational anaesthetic agents (sevoflurane, isoflurane), NTG, and magnesium sulphate and high blood pressure, preexisting bleeding disorders, fibroids, episiotomy, obesity, retained placenta and assisted delivery are all risk factors for PPH.[16,17,18]

The effective strategy to prevent the PPH is active management of the third stage of labor. It also reduces the risk of a postpartum maternal hemoglobin level less than 9 g per dL, and manual removal of the placenta. This practice comprises administration of the oxytocin soon after the delivery of the anterior shoulder, and controlled cord traction (Brandt-Andrews maneuver) to deliver the placenta, and the uterine massage after delivery of the placenta.[19] Placental delivery can be achieved using the Brandt-Andrews maneuver, in which firm traction on the umbilical cord is applied with one hand while the other applies suprapubic counterpressure.[19]

The gold standard for management of PPH is the early diagnosis and activation of a multidisciplinary team to monitor vital signs, laboratory work-up, and therapy must be taken. Generally, the first line management is the use of uterotonic agents.[7] Intravenous oxytocin alone is the recommended first-line uterotonic drug for the treatment of PPH. Oxytocin (10 IU intravenously is recommended for the prevention of PPH.[20] uterotonics like oxytocin, which are designed to cause uterine muscle contraction and are the standard of care globally. it effectively stimulates uterine contractions, which helps to compress blood vessels in the uterus and control bleeding. If oxytocin alone is not sufficient to control bleeding, other uterotonic agents such as methylergometrine 200 µg i.v or IM or and carbetocin 100 µg IM/IV or and oral misoprostol (400–600 µg) and carboprost 250 µg IM or intramyometrially every 15 to 90 minutes for a maximum of 8 doses are recommended for the prevention of PPH**.** In addition, tranexamic acid (TXA) an anti- fibrinolytic is frequently used with uterotonic medications with a dose of 1 g IV over 10 minutes within 3 hours of delivery after PPH diagnosis. The WOMAN trial (World Maternal Antifibrinolytic) is a large, international study that investigated the effectiveness of tranexamic acid in reducing deaths from PPH. The trial has reported that early administration of TXA within 3 hours of birth significantly reduces maternal deaths due to bleeding by about one-third.[21] In life-threatening situations where other options fails, rFVIIa (30-90 mcg/kg) for treating PPH may be considered. However, routine use of rFVIIa for treating PPH is not recommended due to high risk of arterial thromboembolic events.[22]

A bimanual massage with hot sponges and uterotonic medications often effective in control of PPH. The use of bimanual uterine compression or external aortic compression for the treatment of PPH due to uterine atony after vaginal birth is recommended as a temporizing measure until appropriate care is available. However, if these manoeuvres are insufficient to control the bleeding, uterine tamponade may be considered. An intrauterine Bakri balloon tamponade system by filling an intrauterine balloon with 250 to 500 mL of normal saline is used. Uterine tamponade may be useful in those with lower uterine segment atony, where uterotonic agents may have a delayed onset of action and recommended as an effective nonsurgical technique that can potentially improve survival in women with PPH due to uterine atony after ruling out retained products of conception or uterine rupture as a contributing factor.[23] If an intrauterine balloon is not readily available, the uterus may be packed with gauze, or several large Foley catheters may be placed concurrently.

Compression sutures with an absorbing suture (eg, chromic) may also be considered, as they are effective in 90% of cases. However, these manoeuvres can cause uterine necrosis and intrauterine synechiae. Conventional use of uterotonics such as oxytocin, prostaglandins, and medications to support coagulation, such as fibrinogen and tranexamic acid, are helpful but may not be sufficient to arrest life-threatening PPH. In such scenarios uterine packing with a chitosan-covered tamponade is an emerging tool in the armamentarium of the obstetrical team, particularly when resources are limited for advance surgical and other invasive options. However, in extreme cases where bleeding is resistant to these therapies, a hysterectomy may be necessary to avoid possible maternal mortality [1,24,25] It has been observed that the combinations of ergometrine plus oxytocin or misoprostol plus oxytocin may be more effective uterotonic drug strategies for the prevention of PPH ≥500 ml compared with the standard use of oxytocin, but with increased risk of adverse effects (vomiting and hypertension with ergometrine and fever with misoprostol).[26] Surgical interventions include the use of compression suture techniques, uterine and hypogastric artery ligation, and hysterectomy. The priority is to control the bleeding before the patient develops coagulupathy and organ damage from hypo-perfusion.[27]

Some authors have used uterine artery embolization(UAE) to treat the refractory bleeding. UAE is considered a valuable first-line treatment for significant bleeding that doesn't respond to other methods, reducing the need for a hysterectomy due its low invasiveness and high success rate. The uterus also has other blood vessels, so blocking the primary bleeding arteries stops the hemorrhage while keeping the uterus alive. UAE is considered for women experiencing medically refractory uterine atony, birth canal lacerations, or other causes of significant postpartum bleeding. It is particularly beneficial for patients who desire to preserve their fertility. The clinical success rate has been reported as approximately to 85%, and some PPH patients also need ovarian artery embolization in addition to UAE. [28,29]

Dexmedetomidine, significantly a more potent and selective as an alpha-2 adrenergic agonist compared to clonidine, with an alpha-2 to alpha-1 selectivity ratio of 1620:1, while clonidine's 220:1, means less dose is required to achieve the same effect. Dexmedetomidine has applications as an adjunct during neuraxial anesthesia, as well as in general anesthesia (GA) for caesarean delivery. Intravenous infusion of dexmedetomidine is increasingly reported for diverse applications in the field of obstetric anesthesia including light sedation and analgesia, decreased shivering after cesarean delivery,prevention of postoperative nausea and vomiting, and alleviating symptoms of postpartum depression.[30]

Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that binds to receptors in brain and the spinal cord and reduces sympathetic outflow, lowers blood pressure, and may directly increase uterine muscle contractions, helping to prevent the PPH. Activation of these α2-adrenergic receptors leads to an influx of extracellular calcium (Ca^{2+}) into the myometrial cells, likely through voltage-operated calcium channels (VDCCs). It also increases the release of arachidonic acid from the smooth muscle cells. Arachidonic acid then inhibits myosin light chain phosphatase (MLCP), which in turn increases the sensitivity of the contractile elements of the myometrium to calcium. It has an in vitro uterotonic effect, directly increasing the frequency and amplitude of myometrial contractions. However, this effect is observed at concentrations higher than typical therapeutic plasma levels. It is important to note here that dexmedetomidine has been used after cord clamping and in a patient with refractory hypertension, suggesting that it may be considered in complex cases rather than as a universal first-line treatment for PPH. There is a dose-dependent increase in the frequency and amplitude of uterine contractions, when immediately on cord clamping, a loading dose (70 $\mu g.h^{-1}$ over 10 min) of dexmedetomidine is started, followed by maintenance dose of 35 $\mu g.h^{-1}$ I.V. infusion (along with syntocinon infusion).[31]

In some situations, like a cesarean section for pre-eclampsia, drugs used for blood pressure control might also have uterine relaxant effects. Dexmedetomidine could provide a safer alternative to control both blood pressure and bleeding. some authors have reported that dexmedetomidine in a rate 0.4 µg/kg/h shows a significant slowing in heart rate and lowering of the mean arterial blood pressure during caesarean section in preeclamptic patients, it has been also noticed an increased uterine tone and babies are delivered with normal Apgar score. Similarly, literature describes that as dexmedetomidine has a high placental retention, it doesn't cross the placenta to reach the fetus.[9,32,33,34]

We are routinely using dexmedetomidine, intravenous infusion (0.5 to 1 mcg/kg/hr) just before the induction of anaesthesia (general as well as regional) in the OR in patients undergoing elective or emergency caesarean sections in our institute and observed a fast recovery of

uterine tone after administration of oxytocin 5-10 iu and a significant decrease in the incidence of PPH. The authors are of the opine that the dexmedetomidine has uterotonic effects without affecting the fetus status i.e. Apgar score of the newborn. However, more data from large RCT are required for recommendation of regular use of dexmedetomidine in obstetric for improving uterine contractility, apart from the refractory bleeding cases, and its regular use should be encouraged to determine its utility more fully.

CONCLUSION:

Dexmedetomidine has significant multiprong beneficial effects in the patients undergoing obstetric and other non -cardiac surgeries like analgesic, sedative, antihypertensive, antiarrhythmic, postoperative shivering and nausea and vomiting, hemodynamic stability, anaesthetic adjuvant for regional and general anaesthesia**.** Intravenous infusion of dexmedetomidine (0.5-1 mcg/kg/hr) before induction of anaesthesia provides hemodynamic stability lowers the blood pressure and helps in controlling the post-partum bleeding. Further, its uterotonic effect improves the oxytocin effects and provides rapid uterine tone recovery, and so prevents the PPH. Furthermore, It has been suggested that the routine use of dexmedetomidine intravenous infusion (0.5-1 mcg/kg/min) before induction of anaesthesia has no deleterious effects on the fetus, and facilitate the uterotonic effect of oxytocin.In a specific case of a patient with severe, refractory PPH and hypertension after a cesarean section, dexmedetomidine can be used to control blood pressure and uterine bleeding, leading to improved patient outcome. The dexmedetomidine use before or at the time of induction of anaesthesia has no adverse effects on the fetus or the Apgar score of the newborn.

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