Intravenous Carbetocin versus Oxytocin in Management of Placental Delivery in Second Trimester Interruption A Randomized Clinical Trial

Thesis

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List of Abbreviations

ACOG	: American College of Obstetrics and Gynecology
AUC	: Area under the curve
BMI	: Body mass index
CI	: Confidence interval
CS	: Cesarean section
D&E	: Dilatation and evacuation
GA	: Gestational age
HCT	: Hematocrit
I.P	: Intra peretonium
IM	: Intramuscular
IU	: International unit
IV	: Intravenous
MAX	: Maximum
MD	: Mean difference
Min	: Minimum
N	: Number
PG	: prostaglandin
PPH	: Post partum hemorrhage
RCOG	: Royal College of Obstetrics, Gynecology
RR	: Risk ratio
SD	: Standard deviation
TOP	: Termination of pregnancy
US	: Ultrasonography
VA	: Vacuum aspiration
VS	: Versus
WHO	: world health organization

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Introduction

Universal prenatal screening programs have led to an increase in the diagnosis of congenital malformations with subsequent gradual increase in second trimester termination of pregnancy (TOP) ***(Lalitkumar et al., 2007).*** This represents 10–15% of total abortions performed worldwide ***(Newmann et al., 2010).***

Second trimester is the period ranging from 14 – 28 weeks of gestation. It is subdivided into an early period between 14 to 20 weeks and late between 20 to 28 weeks. Termination in the second trimester is more risky than during the first trimester and, therefore; the pharmacologic management seems to be an appealing alternative to surgical evacuation ***(Shabana et al., 2012).***

Complications of the third stage, such as hemorrhage and placental retention requiring surgical evacuation, have received little research attention, despite placental surgical evacuation rates of30-40% being reported ***(von Hertzen et al., 2009).*** Placental retention may be associated with increased blood loss, increased requirement for blood transfusion, anesthetic and operative complications, and infectious morbidity ***(Lalitkumar et al., 2007).***

The high incidence of placental retention, either complete or incomplete, after second-trimester medical pregnancy

termination is an area of clinical concern. Scrutiny of published termination regimens reveals a wide variation in practices between units, although there have been few formal studies on the management of the third stage in medical abortion published ***(Carlan et al., 1997; Leader et al., 2002).*** Placental retention rates vary from 8-80% with significant heterogeneity in uterotonic administration and permissible duration for the third stage ***(Dickinson and Evans, 2002; Bhattacharjee et al., 2008).***

Despite these high rates of placental retention, little attention has been paid to third-stage protocols in the published literature to date. Most units have developed a protocol based on individual clinician opinion and include prophylactic intramuscular syntometrine ***(Ashok et al., 2004),*** intravenous infusion of oxytocin ***(Green et al., 2007),*** intramuscular PGF2α ***(Sundaram et al., 2009),*** nonspecific pharmacologic therapy ***(Dickinson and Evans, 2002),*** and routine curettage postfetal expulsion ***(Carbonell et al., 2008).***

Carbetocin is a synthetic analogue of oxytocin with a longer biologic half-life. As such, it may have advantages over the standard 5-IU intravenous dose of oxytocin given at cesarean delivery once the baby is delivered. The routine 5 IU of oxytocin is frequently augmented by a further infusion of the drug prophylactically against postpartum hemorrhage in patients the surgeon considers to be at high risk ***(Kent, 2010).***

A report by ***Attilakos and colleagues (2010)*** showed that 100μg of carbetocin was more effective than an ampoule of5 IU oxytocin in reducing the need for additional oxytocin infusions. There were no differences in the incidence of hemorrhage or blood transfusion requirements. Despite its higher cost, carbetocin may find a place in the armamentarium of uterotonic agents used in obstetrics.

Current evidence shows that carbetocin significantly reduces the need for therapeutic uterotonics compared to placebo and oxytocin in women undergoing caesarean delivery. Carbetocin results in a reduced need for uterine massage post delivery in both caesarean ***(Attilakoset al., 2010; Higgins et al., 2011; Larciprete et al., 2013)*** and vaginal deliveries ***(Boucher et al., 2004).*** In fact, one of the recommendations from The Society of Obstetricians and Gynaecologists of Canada for prevention of postpartum hemorrhage is that carbetocin, 100 μg given as an intravenous bolus over one minute, should be used instead of continuous oxytocin infusion in elective caesarean section for the prevention of PPH and to decrease the need for therapeutic uterotonics ***(Su et al., 2012).***

There is no previous study about using Carbetocin in management of postabortive bleeding; so this study considered the first study in this respect.

Aim of the Work

The aim of this study is to:

1. Comparison between the efficacy 100 μg intravenous Carbetocin and the efficacy of 20 IU intravenous infusion Oxytocin in the prevention of a placental retention in 2nd trimester medical termination.

2. Comparison between the efficacy of 100 μg intravenous Carbetocin and the efficacy of 20 IU intravenous infusion Oxytocin in reducing postdelivery blood loss.

3. Comparison between carbetocin group and oxytocin group as regard the severity and frequency of side effects.

Methods of Induced Mid-trimester Abortion

Abortion is defined as 'termination of pregnancy (TOP) by any means before the fetus is viable'. Viability is now considered to be reached at 23–24 weeks of gestation. Second trimester, or midtrimester, is a period ranging from 13 to 28 weeks of gestation, which again is subdivided into an early period between 13 and 20 weeks and a late period between 20 and 28 weeks ***(Lalitkumar et al., 2007).***

TOP by induced abortion is practiced worldwide. Induced abortion, either elective or therapeutic termination of a viable pregnancy, is one of the most ancient procedures. Of the 210 million pregnancies that occur each year, >46 million (22%) end in induced abortions ***(Alan Guttmacher Institute, 1999).*** A majority (90%) of the terminations take place in the first trimester. Worldwide mid-trimester abortion constitutes 10–15% of all induced abortions but is responsible for two-thirds of all major complications ***(WHO, 1997).***

Although the majority of abortions are performed in the first trimester, there is still a gradual increase in second-trimester abortion because of the wide scale introduction of prenatal screening programs detecting women whose pregnancies are complicated by serious fetal abnormalities such as cardiovascular and skeletal malformation ***(Lalitkumar et al., 2007).***

Over the last 20 years, there have been continuing efforts to improve the abortion technology in terms of effectiveness, decreasing rates of complications, technical ease of performance and acceptability. During this time, more than 20 countries have partially or fully liberalized their abortion laws ***(Berer, 2004).*** Today, in almost all countries, the law permits abortion to save a pregnant woman's life. However, the requirement of legalization is no guarantee for a safe abortion. In many countries where abortion is illegal, as in Latin America, private physicians often perform safe abortions for relatively high medical fees, and the law is rarely enforced ***(Fathalla, 1997).***

Background

Abortion dates back to the period of Socrates, Plato, Aristotle and Hippocrates ***(Anonymous, 1995).*** Different surgical and medical methods of abortion have been used since the early age. Surgical abortion is one of the oldest and most commonly practiced techniques in many parts of the world. A matter of great concern was that there were no safe drugs for inducing an abortion. Since ancient time, women have used various herbs, salts, douches and purgatives, all with questionable success to achieve pregnancy termination ***(Riddle et al., 1993).*** In recent years, effective medical abortion methods with low morbidity have been emerging and become better accessible ***(Lalitkumar et al., 2007).***

In the early 1970s, the most commonly used methods were vacuum aspiration (VA), dilatation and curettage, sharp curettage, hysterotomy (sectio parva), intra-amniotic injection of hypertonic saline or hyperosmolar urea, intra- or extra-amniotic administration of ethacryidine lactate (Rivanol), parenteral, intra-amniotic or extra-amniotic administration of prostaglandin (PG) analogues and i.v. or i.m. administration of oxytocin***(WHO, 1997).***

Rivanol is a dye with antiseptic properties and seems to be less toxic than hypertonic saline. As with hypertonic saline, Rivanol stimulates endogenous PG and thromboxane production, probably because of chemical trauma to the fetal membranes and the decidua, promoting cervical priming and initiating labour. The instillation to delivery interval ranged from 25 to 40 h ***(Ingemarsson, 1979; Bhathena et al., 1990; Blumenthal et al., 1999)*** which could be reduced to 15–20 h with concomitant use of oxytocin ***(Yapar et al., 1996).***

Among the drawbacks of all these medical methods are the need for puncture of the intra-amniotic space or the introduction of a Foley catheter into the extra-amniotic space, a relatively long induction-to-abortion interval and the need for curettage after the expulsion of the fetus ***(Bygdeman, 1983).*** The i.v. infusion of oxytocin was inconvenient to use because of the serious side effects of water intoxication. The risk of disseminated intravascular coagulation with hypertonic saline is 0.8%***(Edelman et al., 1976).*** This is because of rapid intravascular absorption of

hypertonic saline from the amniotic cavity or inadvertent i.m. or i.p. injection of saline resulting in hypernatremia and necrosis of the affected tissue. Thus, many of these methods were very cumbersome in respect of their side effects and medical expertise required.

With the introduction of PGs and later PG analogues, the efficacy of medical abortion could be improved, and the risk for complications and side effects was reduced. The method of medically induced abortion could be further improved as mifepristone became available in the 1980s ***(Bygdeman and Swahn, 1985; Urquhart and Templeton, 1987; Swahn and Bygdeman, 1988; Silvestre et al., 1990; Gottlieb and Bygdeman, 1991).*** With mifepristone, the induction-to-abortion interval was shortened, and the dose of PG analogues required was reduced. Today, medical abortion is the method of choice in many centres ***[Royal College of Obstetricians and Gynaecologists (RCOG), 1997]***.

PGs and PG analogues

PGs play an important role in the regulation of uterine contractility during pregnancy ***(Mitchell, 1987).*** The receptors are present throughout the pregnancy; hence, PGs and their analogues are effective for TOP. Naturally occurring PGs, mainly prostaglandin El (PGE1), PGE2 and PGF2α, are potent stimulants of uterine contractility at any stage of pregnancy and also cause cervical ripening and dilatation. However, because of the rapid metabolism and high incidence of gastrointestinal side