Vaginal Misoprostol versus Carbetocin in Decreasing Blood Loss in Abdominal Myomectomy: Randomized Controlled Trial

Thesis

Submitted for Partial Fulfillment of Master Degree in Obstetrics and Gynecology

By

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2019

Acknowledgment

First and foremost, I feel always indebted to ALLAH, the Most Kind and Most Merciful.

I'd like to express my respectful thanks and profound gratitude to ***Prof. Amro Salah Elhoussieny,*** *Professor of Gynecology and Obstetrics - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Prof. Mohamed El-Mandooh Mohamed,*** *Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to ***Dr. Heba Abd El-Basset Allam,*** *Lecturer in Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

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List of Abbreviations

Abb.	Full term
BMI	*Body mass index*
CI	*Confidence interval*
CLT-M	*Conventional laparotomy for myomectomy*
Hb	*Hemoglobin*
HCT	*Hematocrit*
IQR	*Interquartile range*
ISM	*In situ morcellation*
IV	*Intravenous*
LA-MLT	*Laparoscopically assisted minilaparotomy*
MLT	*Minilaparotomy*
MLT-M	*Minilaparotomy for myomectomy*
PPH	*Postpartum hemorrhage Intramuscular*
SD	*Standard deviation*
SOGC	*Canadian Society of Obstetricians and Gynecologists*
UMLT-M	*Ultra-minilaparotomy for myomectomy*
WHO	*World Health Organization*

INTRODUCTION

Myomectomy is one of the curative treatment options for many uterine fibroids, but substantial intraoperative blood loss and the requirements for blood transfusion remain major consideration for abdominal myomectomy ***(Levy, 2008).***

Three common causes of increased blood loss during abdominal myomectomy are poor surgical technique, the complexity of intra-abdominal pathology (such as low corpus, intra- ligamentous myomas, or obliteration of cul-de-sac), and the excessive loss of intrauterine blood during dissection of the myomas ***(Mukhopadhaya et al., 2008).***

Numerous strategies to reduce blood loss during abdominal myomectomy have been reported ***(Kongnyuy et al., 2011).***

Early reports described mechanical occlusion of the uterine arteries using myomectomy clamps and per cervical rubber tourniquet. GnRH agonists before surgery seem to be effective in some indications ***(Lin, 2011).***

Preoperative uterine artery embolization decreases blood loss during myomectomy, but this technique is restricted to particular hospital centers and can be complicated ***(Lin, 2011).***

Laparoscopic uterine artery occlusion has been described as a treatment for symptomatic myomas ***(Holub et al., 2007).***

Recent studies indicated that vaginal misoprostol was beneficial in significantly reducing perioperative blood loss during myomectomy. Despite these procedures, excessive hemorrhage during abdominal myomectomy remains a challenge to gynecologic surgeons ***(Istre, 2008).***

Misoprostol, a synthetic prostaglandin E1 analogue, apparently reduces to uterine blood flow, it stimulates uterine contractions and this leads to contraction of the vessels supplying blood to the leiomyomas. This subsequently may redistribute the blood from the diseased uterus back to the circulation, hence reducing operative blood loss during abdominal myomectomy, there is a moderate quality evidence that misoprostol reduces blood loss by between 70,24ml and 125.25 ml ***(Shokeir et al., 2013).***

Carbetocin is a long- acting synthetic analogue of oxytocin with a half-life of 40 minutes and 80% bioavailability in IM injection. After IM or IV administration of this drug, uterine contractions start in less than 2 minutes ***(Sweeney, 1990).*** Carbetocin makes a longer uterine response compared with oxytocin in terms of frequency and amplitude of contractions ***(Hunter, 1992).***

Recent studies showed that oxytocin infusion and carbetocin may be beneficial in reducing blood loss during myomectomy ***(Yang et al., 2012).***

AIM OF THE WORK

Aim of the work is to evaluate the efficacy of administration of carbetocin in comparison to vaginal misoprostol in decreasing blood loss in women undergoing abdominal myomectomy.

Chapter 1
CARBETOCIN

Introduction

Carbetocin (1-deamino-1-carba-2-tyrosine(*O*-methyl)-oxytocin) is a long-acting synthetic oxytocin agonist ***(Amornpetchakul et al., 2018).***

Carbetocin is a newer agent that can potentially provide the benefit of longer acting maintenance of oxytocic action without the need for post-delivery infusion. It has been approved for the prevention of uterine atony in over 70 countries and in the UK is indicated for the prevention of uterine atony following delivery of the infant in caesarean delivery where spinal or epidural anaesthesia has been used. However, it has not been approved in the UK for use following vaginal birth ***(Meshykhi et al., 2016).***

The half-life of carbetocin is 40 min, which is 4- to 10-fold longer than the half-life of oxytocin ***(Amornpetchakul et al., 2018).***

The onset of action occurs within 2 min, and the duration of action is 1 and 2 h after intravenous and intramuscular injection, respectively ***(Meshykhi et al., 2016).***

A dose of 100 mcg of carbetocin is generally considered to be equivalent to 5 U of oxytocin ***(Cordovani et al., 2012).***

The pharmacodynamic activity of oxytocin and carbetocin is similar in that they both bind to oxytocin receptors within the myometrium and effectuate rhythmic uterine contractions. Carbetocin also increases the amplitude of uterine tone and the frequency of existing uterine contractions ***(Amsalem et al., 2014).***

Pharmacology

Carbetocin was initially developed in the 1970s as a veterinary product; it is a long-acting synthetic octapeptide analogue of oxytocin (which is a nonapeptide) with agonist properties at the oxytocin receptor. Structural differences to oxytocin include replacement of the amino- group of cystein by a hydrogen atom, modification of the disulphide bond by a thio-ether bond and a substitution of the hydroxyl group of tyrosine by a methyloxyl group. These molecular changes give carbetocin more stability and avoid early decomposition by disulphidase, aminopeptidase and oxidoreductase enzymes (Fig. 1) ***(Meshykhi et al., 2016).***

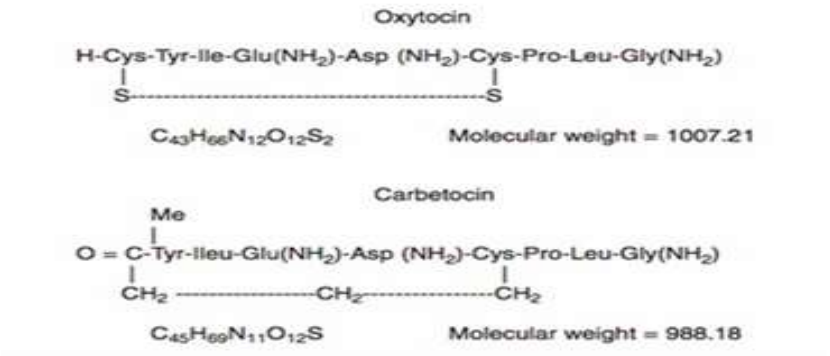

Figure (1): Chemical formula of oxytocin and carbetocin
(Meshykhi et al., 2016)

The pharmacodynamics properties of carbetocin are comparable to those of endogenous oxytocin. Carbetocin selectively binds to oxytocin receptors in the smooth muscle of the uterus resulting in rhythmic uterine contractions, increased frequency of existing contractions, and increased uterine tone ***(Kramer et al., 2013)***.

Early pharmacokinetic studies in non-pregnant women suggested that the half-life of carbetocin when given intravenously was 42 ± 9 minutes, up to 10 times longer than that of oxytocin ***(Westhoff et al., 2013).***

Intravenous injection of carbetocin 8–30 μg produced a tetanic uterine contraction within two minutes that lasted about six minutes, and was followed by rhythmic contractions for a further 60 ± 18 min; intramuscular injection of carbetocin 10–70 μg also produced tetanic contraction in less than two minutes but lasted for about 11 minutes, and was followed by rhythmic contractions for an additional 119 ± 69 min. The time required for absorption from the intramuscular route may account for this difference but in addition carbetocin is a more lipophilic agent ***(Tsen et al., 2010).***

The effects of carbetocin on uterine muscle have been evaluated in vitro. The contractile effects of a variety of uterotonic agents, including oxytocin and carbetocin, used in the management of PPH have been investigated in myometrial strips from pregnant women ***(Weale et al., 2013).***

The authors measured and compared the potency and maximal response valueusing maximal amplitude and mean contractile force as indices of contraction. Single, EC50 concentrations of the drugs were administered after which both force and contraction peak parameters were compared. A wide difference in potencies using both measures of contractility was noted, with oxytocin and carbetocin being the most potent ***(George et al., 2010).***

A prospective study examining the effects of intramuscular carbetocin versus oxytocin in women 24–48 hours postpartum found a significantly prolonged duration of activity for carbetocin. An intrauterine pressure transducer was used to measure frequency, amplitude and duration of contractions following the administration of either oxytocin 10 U or carbetocin 30 μg. Carbetocin resulted in contractions of sustained higher amplitude and frequency, with the initial pattern of hypertonic activity peaking at 60 minutes with a mean frequency if 4.09 contractions/10 min in the first 60 minutes. In contrast oxytocin induced an initial pattern of hypertonic activity peaking at 20 minutes with a mean frequency of 4.55 contractions/10 min in the first 60 minutes ***(Carvalho et al., 2004).***

In another in vitro study, Cole et al. examinedthe contractile response effect of oxytocin and carbetocin on human myometrium after pre- exposure to oxytocin. They found a decreased contractile response to both carbetocin and

oxytocin, most likely as a result of the desensitization phenomenon ***(Cole et al., 2016).***

The pharmacokinetic properties of carbetocin allow for its use as a single bolus dose; there is a biphasic elimination pattern after intravenous injection in the prescribed dose range, with a terminal elimination half-life of approximately 40 minutes due to modification of the molecular structure of the drug which confers lipophilic properties and stability against aminopeptidase, oxidoreductase and disulphidase enzymatic cleavage, prolonging its pharmacological effects. By comparison, the terminal half-life of oxytocin is around five minutes. Renal clearance of the unchanged form is low, with <1% of the injected dose excreted unchanged by the kidney. Small amounts of carbetocin have been shown to pass into breast milk following single bolus dosing, but it is assumed to be degraded in the infant gut ***(Meshykhi et al., 2016).***

Clinical dose-finding studies have largely been confined to women undergoing elective caesarean delivery. Two studies in pregnant women at term, undergoing caesarean delivery and with low risk of PPH, found that a dose as low as 20 μg was effective ***(Cordovani et al., 2012; Anandakrishnan et al., 2013)***. These studies used doses ranging from 20–120 μg and found a high incidence of hypotension (55% and 42.5%). Another, double-blind, dose-finding study of women undergoing elective caesarean delivery under spinal anaesthesia investigated the intravenous dose of carbetocin required to