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ORIGINAL ARTICLE

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Uterotonic drug usage in Canada: a snapshot of the practice in obstetric units of university-affiliated hospitals

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ABSTRACT
Objective: The objective of this study was to determine the pattern of uterotonic drug usage in obstetric units of university-affiliated hospitals in Canada.
Methods: This was a prospective observational study conducted in the form of an electronic survey. The target group consisted of chiefs or directors of Obstetrics and Anaesthesia at university-affiliated hospitals across Canada. The survey was sent out between November 2016 and January 2017, using the program 'SurveyMonkey'. Data on institutional obstetric practices and usage of uterotonic agents were collected.
Results: The survey was sent to 92 obstetricians and anesthesiologists from 46 institutions, of which 33 clinicians from 24 institutions responded. About 65% of clinicians were unaware of the rate of postpartum hemorrhage in their institution. The first-line agent for vaginal deliveries was reported as oxytocin by 94% and carbetocin by 6% of physicians. For women at low-risk for postpartum hemorrhage when undergoing cesarean deliveries (CD), 66% reported oxytocin as the first-line uterotonic, while 34% reported carbetocin. For CDs at high-risk of postpartum hemorrhage, 60% of physicians reported oxytocin and 40% reported using carbetocin initially. The use of second-line uterotonics was also variable. The choice of uterotonic was mainly based on perceived efficacy and Society of Obstetricians and Gynaecologists of Canada guidelines.
Conclusion: There is a lack of a unified approach to the use of uterotonic drugs for postpartum hemorrhage management in Canada. To improve the management of postpartum hemorrhage due to uterine atony, an evidence-based approach to usage and consensus between obstetricians and anesthesiologists is warranted.

Keywords: Uterotonic drugs; Carbetocin; Academic institutions; Survey; Practices

Introduction

In Canada and the United States, the incidence of severe postpartum hemorrhage (PPH) related to uterine atony appears to be on the rise, despite the use of oxytocin and other uterotonic agents.[1,2] This has resulted in an increase in the rates of blood transfusion and hysterectomy.[2] Postpartum hemorrhage continues to be one of the leading causes of maternal morbidity and mortality worldwide.[3]

Uterotonic agents are used to prevent and treat PPH. Oxytocin, the most common first-line uterotonic, is routinely used in the third stage of labor for vaginal deliveries, as well as for elective and emergency cesarean deliveries (CD).[4] Carbetocin, an oxytocin analogue, is also used instead of oxytocin in some countries, including Canada. In fact, the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends carbetocin as the uterotonic agent of choice to prevent PPH at elective CD (1-B recommendation).[5] The SOGC also recommends its use for women delivering vaginally with one risk factor for PPH (1-B recommendation).[5]

Second-line uterotonics are recommended if uterine atony persists despite prophylaxis or treatment with oxytocin or carbetocin.[5–8] These uterotonics include ergonovine maleate, carboprost and misoprostol. Recently, Bateman et al.[9] looked at patterns of second-line uterotonic usage for the treatment of uterine atony across the United States. They observed a surprisingly high level of inter-hospital variation that could not be explained by patient or hospital characteristics. There

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is also a wide variability in the current national and international guidelines for uterotonic usage in the management of PPH.[4–8] This suggests a lack of consensus for both first-line and second-line uterotonic utilization.

The pattern of uterotonic drug usage in Canada is currently unknown and may be more varied and complex due to the presence of carbetocin as an alternative to oxytocin. The objective of this study was to determine the pattern of uterotonic usage in obstetric units of university-affiliated hospitals in Canada.

Methods

In Canada, no large databases exist to track usage of uterotonics in hospitals. Therefore, we conceived a prospective observational study in the form of a targeted, online survey. Research Ethics Board approval was obtained from Mount Sinai Hospital, Toronto, Canada (REB16-0239-E; September 26, 2016). Our target group consisted of chief obstetricians and directors of obstetric anesthesia (or chief anesthesiologists in lieu) at all 46 obstetric units of university-affiliated hospitals across Canada. Their email addresses were obtained via medical school/university hospital websites. If no email address was found or accessible, an administrative assistant at each respective university was contacted to obtain the email address of the chief of obstetrics and/or obstetric anesthesiology. In certain cases there were 'interim chiefs' and 'co-chiefs' of the departments, and referrals were made to the appropriate person in the institution to complete the survey. For this reason, a total of 109 surveys were sent out, to target 92 clinicians from 46 hospitals. An invitation letter explaining the study was sent via email to the practitioners, along with a link to the survey, which included the study questions integrated into the program 'Survey Monkey' (SurveyMonkey® Canada – Surveymonkey.com) (Appendix 1, supplementary file). The consent to participate was implied if the person contacted agreed to respond to the survey. The survey questions were phrased to aim mainly at institutional, rather than individual, clinical practice. The survey was distributed during the period November 2016 to January 2017. Three reminder emails were sent at approximately one week intervals from the initial send out date.

Data collected consisted of institutional characteristics, use of oxytocin versus carbetocin in both vaginal and CD in women at low- and at high-risk for PPH; and use of second-line uterotonics. For the purpose of this study, the following risk factors for PPH were provided as a reference to responders of the survey: abruptio placentae, placenta previa, placenta accreta/increta/percreta, uterine rupture, polyhydramnios, fetal macrosomia, multiple gestation (twins/triplets), grand multiparity, preeclampsia, oxytocin induction/augmentation for prolonged period, infection (e.g. chorioamnionitis), morbid obesity (body mass index >40 kg/m^2), instrumental delivery, bleeding disorders (pregnancy and non-pregnancy related), general anesthesia and previous history of PPH. Data were collected and integrated into Excel format for analysis. Data were summarised as proportions of respondents.

Results

The survey targeted 92 clinicians across all 46 university-affiliated hospitals in Canada. A total of 33 clinicians from 24 hospitals responded, giving us individual and institutional response rates of 36% and 52%, respectively. We received responses from all provinces except for Saskatchewan. Of the 33 respondents, 61% were anesthesiology specialists and 39% were obstetricians. The majority of the respondents had practice experience of more than five years in their area of specialty. Most participants (76%) reported CD rates of 21–30%, with a few (24%) reporting rates over 30%. Epidural rates were high across most institutions, with 42% of respondents reporting rates greater than 75%. The majority of clinicians (64%) were unaware of the rate of PPH in their institution (Table 1).

First-line uterotonic agents

Oxytocin was reported as the first-line uterotonic drug for vaginal delivery by 94% (31/33) of responders, and for low-risk and high-risk CD by 66% (21/32) and 60% (18/30) of responders, respectively. Carbetocin was reported to be the first-line agent for vaginal delivery by only 6% (2/33) of responders, but for low-risk and high-risk CDs by 34% (11/32) and 40% (12/30) of responders, respectively (Table 2).

For vaginal deliveries, the most commonly used dose of oxytocin included a 5 IU intravenous (IV) bolus or 10 IU intramuscular bolus. For both low- and high-risk CD, most participants reported the use of an IV oxytocin bolus of 5 IU (range 3–10 IU) in their institutions, however, maintenance infusion rates post-bolus differed. Sixty-two percent (8/13) of obstetricians used oxytocin boluses in addition to an infusion, even for low risk CD. Rapid boluses were used for vaginal (30%) as well as both low- and high-risk CD (13%). Oxytocin boluses of 10 IU, either IV or intramuscularly, were used by 20% (4/20) of anesthesiologists and 38% (5/13) of obstetricians for vaginal deliveries. While for CD, 10% (2/20) of anesthesiologists and 38% (5/13) of obstetricians used 10 IU IV boluses. The dose of carbetocin ranged from 25 to 100 μg IV for almost all types of deliveries (Table 3).

Second-line uterotonic agents

The second-line uterotonic usage was highly variable, with the use of carboprost by all, and ergonovine and

Table 1 Institutional obstetric data

	Overall (N=33)	Anesthesiologists (N=20)	Obstetricians (N=13)
Duration of practice of responding clinicians (years)			
<5	1 (3.0)	1 (5.0)	0 (0)
5–10	9 (27.3)	9 (45.0)	0 (0)
10–20	10 (30.3)	5 (25.0)	5 (38.5)
>20	13 (39.4)	5 (25.0)	8 (61.5)
Number of deliveries/year			
2500–4999	17 (51.5)	10 (50.0)	7 (53.8)
>5000	16 (48.9)	10 (50.0)	6 (46.2)
Cesarean delivery rate			
21–30%	25 (75.8)	17 (85.0)	8 (61.5)
>30%	8 (24.2)	3 (15.0)	5 (38.5)
Epidural rate (%)			
<25	1 (3.0)	1 (5)	0 (0)
25–50	3 (9.1)	1 (5)	2 (15.4)
51–75	15 (45.5)	9 (45)	6 (46.2)
>75	14 (42.4)	9 (45)	5 (38.5)
Postpartum hemorrhage rate (%)			
<3	4 (11.8)	3 (15.0)	1 (7.7)
>3	8 (23.5)	1 (5.0)	7 (53.8)
Unknown	21 (63.6)	16 (80.0)	5 (38.5)

Values are n (%).

Table 2 Use of first and second-line uterotonic drugs

First-line uterotonic agent	Overall (N=33)	Anesthesiologists (N=20)	Obstetricians (N=13)
Oxytocin			
Vaginal	31 (94)	18 (90)	13 (100)
Low-risk CD	21 (66)*	11 (58)§	10 (77)
High-risk CD	18 (60)*	11 (61)§	7 (58)
Carbetocin			
Vaginal	2 (6)	2 (10)	0 (0)
Low-risk CD	11 (34)*	8 (42)§	3 (23)
High-risk CD	12 (40)*	7 (39)§	5 (42)
Second-line uterotonic agent	**Overall (N=29)**	**Anesthesiologists (N=18)**	**Obstetricians (N=11)**
Additional oxytocin	17 (59)	12 (67)	5 (46)
Additional carbetocin	2 (7)	1 (6)	1 (9)
Carboprost	29 (100)	18 (100)	11 (100)
Ergonovine maleate	23 (79)	13 (72)	10 (91)
Misoprostol	23 (79)	13 (72)	10 (91)

*N=32 for low-risk CD. *N=30 for high-risk CD. §N=19 for low-risk CD. N=18 for high-risk CD. Values are n (%). CD: Cesarean delivery.

misoprostol each by 79% of responders (Table 2). Amongst the second-line drugs, carboprost was ranked as the top choice overall, followed by ergonovine by anesthesiologists and misoprostol by obstetricians. All responders used a carboprost dose of 250 μg, and a maximum of eight doses (range 2–8), with boluses given at least 15 minutes apart. For ergonovine, the doses used were 200–250 μg, either IV or intramuscular, with variable timing intervals between repeat doses, ranging from five minutes to four hours.

Choice of drugs

The top ranked reasons as to why clinicians chose their first or second-line uterotonic drugs were the agent's perceived efficacy, the SOGC guidelines or obstetricians' preference, and the convenience. There were nine institutions with paired responses from an anesthesiologist and an obstetrician. For the first-line uterotonic agent, the agreement between the responses of the anesthesiologists and the obstetricians was 81%, while for the

Table 3 Mode of administration and doses of oxytocin and carbetocin at delivery by all practitioners

	Vaginal delivery (N=33)		Low-risk CD (N=32)		High-risk CD (N=30)	
Oxytocin	N (%)	Dose	N (%)	Dose	N (%)	Dose
IM (IU)	5 (15.2)	10 (5–10)	0 (0)	NA	0 (0)	NA
IV bolus (IU)	5 (15.2)	5 (5–10)*	0 (0)	5 (3–10)*	0 (0)	5 (3–10)*
IV bolus + infusion	8 (24.2)	–	11 (34.4)	–	9 (30.0)	–
IV infusion (IU/L)	11 (33.3)	20 (20–40)	10 (31.3)	20 (20–60)	9 (30.0)	40 (20–40)
IM + infusion	2 (6.1)	–	0 (0)	–	0 (0)	–
Carbetocin	N (%)	Dose	N (%)	Dose	N (%)	Dose
IV bolus (μg)	2 (6.1)	100 (100–100)	11 (34.4)	100 (25–100)	12 (40.0)	100 (50–100)

CD: cesarean delivery. IM: intramuscular. IV: intravenous. IU: international units. Dose expressed as median (range).
*Represents IV bolus of oxytocin alone or with infusion.

second-line uterotonic agent, it was only 22%. For doses and routes of oxytocin administration, the agreement was 40%.

Discussion

To our knowledge, this is the first Canadian study using a survey to establish patterns of uterotonics usage in obstetric units of Canadian academic hospitals. Our findings suggest that oxytocin remains the predominant first-line uterotonic drug. Carbetocin was also found to be widely utilized in all types of deliveries, primarily in CD; however, its indications and doses were not consistent with SOGC guidelines.[5] The use of second-line uterotonic drugs was also highly variable and dependent upon the drug's perceived efficacy and the obstetrician's preference. These findings warrant a review of evidence-based literature and application of appropriate guidelines for consistency in the management practices across the country.

Regarding oxytocin usage, our results are in keeping with previous surveys conducted in other countries that have confirmed great variability in oxytocin management between obstetricians and anesthesiologists;[10] the importance of implementing national guidelines for oxytocin use to improve patient safety and reduce side effects;[11] and a potential lack of robust evidence/research in the area of uterotonic management, as evidenced by a perception that oxytocin boluses and infusions are 'low-risk'.[12,13] Our results further elucidate practices regarding second-line uterotonic usage, reflecting lack of consistency in drug choices and usage, similar to the findings in the United States.[9]

Oxytocin

Although it is common to use a 5 IU bolus IV for all types of deliveries, 10 IU boluses are also used. It may be reasonable to give a higher dose, up to 10 IU in patients at high-risk for PPH, or in the event of uterine atony, however, this dose should be given in aliquots of smaller doses.[14] Such doses are, however, not recommended for routine prophylaxis for vaginal and low-risk CD. These higher doses have been shown to produce a high rate of hypotension, tachycardia and dysrhythmia. Therefore, higher doses of oxytocin should be used with caution, especially in the presence of neuraxial blockade or hypovolemia secondary to PPH, where the side effects can be more pronounced.[14] What is more concerning is that our findings suggest that oxytocin 10 IU IV is used in vaginal deliveries despite a lack of routine cardiac monitoring or the presence of anesthesia personnel. Intravenous boluses of oxytocin 5–10 IU are also still commonly used for CDs, despite established evidence against it. The effective dose 90% (ED90) for an IV bolus of oxytocin is 0.35 IU (95% confidence interval (CI) 0.18 to 0.52 IU) at elective CD and 2.99 IU (95% CI 2.32 to 3.67 IU) at CD for labor arrest.[15,16] Butwick et al.[17] also suggested that doses between 0.5 and 3 IU are effective at elective CD and that a dose of 5 IU can no longer be justified. Oxytocin infusions are often used alone or in conjunction with IV boluses for elective CD and CD for labor arrest. Recently published evidence from a randomized controlled trial by Duffield et al.[18] confirms that high rate oxytocin infusion (15 IU/h) versus low rate (2.5 IU/h) at elective CD does not improve uterine tone or reduce PPH rate and that the lower maintenance rate may minimize oxytocin side effects. Women with prior exposure to oxytocin for labor augmentation or induction undergoing CD for labor arrest require a higher infusion rate (ED90 44.2 IU/h, 95% CI 33.8 to 55.6) compared to their non-laboring counterparts (ED90 16.2 IU/h, 95% CI 13.1 to 19.3).[19] The study by Lavoie et al.[19] illustrates that higher doses of oxytocin and more second-line uterotonics are required in women with labor arrest and previous oxytocin exposure. However, it is the opinion of the authors that these high oxytocin infusion rates (and therefore total doses) should be interpreted with caution. These doses are not the norm at our institution. Furthermore, the authors believe that more teaching regarding oxytocin pharmacology and its side effects should be provided to labor and delivery nurses, obstetricians and family doctors so that, in the setting of PPH prevention, the benefit may be maximized and side effects minimized.

Carbetocin

Carbetocin was used in vaginal deliveries as well as high-risk CD. This is despite no recommendations in SOGC guidelines for its use in high-risk CD.[5] The use of carbetocin at vaginal deliveries was reported in only 6% institutions, so significance and generalizability of this finding must be guarded. Carbetocin doses ranged from 25 to 100 μg. The product monograph for DURATOCIN™ recommends 100 μg, but the evidence suggests the ED90 for elective CD is 14.8 μg (95% CI 13.7 to 15.8) and that doses >100 μg may be required for CD after labor arrest (ED90 121 μg, 95% CI 111 to 130), but that such doses may induce arrhythmias and cannot be recommended.[20,21] Carbetocin is not currently recommended by any national guideline other than that of the SOGC.

Second-line uterotonics

Our survey findings convey that second-line uterotonic usage for PPH management is also variable in Canadian centers. Use of carboprost, ergonovine maleate and misoprostol is based on clinician preference and experience more than evidence. This is akin to the 'institution-based factors' such as practitioner experience, preference and local hospital culture described by Bateman et al.[9] The doses of both carboprost and ergonovine were consistent with SOGC guidelines,[5] however, the frequency of administration of ergonovine maleate was quite varied. Additional carbetocin was used in the event of continued uterine atony despite lack of evidence or guideline recommendations.[5,7,8] Both obstetricians and anesthesiologists considered carboprost to be their first choice for a second-line uterotonic, however, we were surprised to find out that obstetricians chose misoprostol over ergonovine as their second choice second-line uterotonic, in the event of PPH. This could perhaps be because the management of obstetricians is geared towards vaginal delivery, while anesthesiologists consider parenteral routes in the setting of CD. Misoprostol has been shown to have significant side effects (cramping, hyperthermia, shivering, convulsions, diarrhea, fever) and has limited efficacy.[22,23] The advantage of ergonovine is that it can be given both IV and intramuscularly, as per the SOGC and the Royal College of Obstetricians and Gynaecologists (RCOG).[5,7] Also, ergonovine has been associated with a reduced risk of hemorrhage-related morbidity during CD as compared to carboprost.[24] Dose-response studies done in human myometrial samples from laboring and non-laboring women also show that ergonovine provides superior contraction compared to carboprost and misoprostol.[25] Therefore we believe that ergonovine may be the best choice for a second-line uterotonic in the absence of contraindications such as hypertension or preeclampsia.

Canadian Guidelines

National guidelines are vital to the evidence-based practice of clinicians. Inconsistencies in societal guidelines continue to contribute to significant variations in the clinical uterotonic regimens used for vaginal and CD, whether elective or for labor arrest. Bohlmann et al.[6] and Dalkhe et al.[4] both elaborated on the substantial variation in medical approaches to PPH prevention and treatment, as well as resuscitation strategies, in various international guidelines. Postpartum hemorrhage remains one of the leading worldwide causes of morbidity and mortality.[3] This is confirmed by the latest MBRRACE-UK report (2017), which found that death from hemorrhage has doubled from 2009–11 to 2013–15.[26] This underscores the need for improved national and international uterotonic guidelines.

The choice of first- and second-line agents for PPH in our survey was mainly based on the perceived efficacy and the SOGC guidelines or obstetrician's preference. Interestingly, these particular guidelines are the only ones recommending carbetocin 100 μg in lieu of oxytocin, administered over one minute for elective CD or vaginal delivery, when there is one risk factor for PPH (not specified) (Appendix 2, supplementary file).[4,5] There is, however, more recent evidence that suggests smaller doses are equally effective in elective CD, while eight-times higher doses are required for CD during labor arrest.[20,21] The SOGC recommended oxytocin dosing for medical management of established PPH is 10 IU intramuscular, 5 IU IV push, or 20–40 IU in 250 mL normal saline IV infusion at 500–1000 mL/h.[4,5] Although ergonovine doses and formulations differ between guidelines and countries,[4,5,7,8] in Canada ergonovine 0.25 mg is recommended via the intramuscular or IV route, repeated every two hours. The guidelines regarding carboprost administration are consistent across countries, with the recommendation of 0.25 mg intramuscularly (or intramyometrially in Canada), which can be repeated every 15 minutes to a maximum of 2 mg (eight doses).

So where do we go from here? College and societal guidelines can have far reaching influence and impact both academic centers and small community hospitals alike. Therefore, it is of the utmost importance that these guidelines be consistent, concise and offer a clear message to practising clinicians. The authors feel that the SOGC guidelines, as well as their international counterparts from the American College of Obstetricians and Gynecologists (ACOG) and RCOG, are vital aids to evidence-based practice of clinicians. Therefore, the authors recommend that evidence from dose-finding studies in various patient populations and recent literature[11–19] be used to update such guidelines. Ideally the SOGC, RCOG and ACOG should consider working together to develop guidelines.

Our study has significant limitations that should be recognized. Individualized institutional response rates of 36% and 52%, respectively, although in keeping with some other responses noted for surveys in the literature, are very low. Therefore, any conclusions drawn may not be generalizable, particularly to institutions outside Canada. However, the majorities of respondents were from large academic centers with annual delivery rates of more than 5000, and hence may provide a good overview of practices across the country. Survey methodology also has inherent survey and selection bias, as respondents' practices are likely to differ from those who do not respond. Furthermore, anesthesiologists were over-represented when compared to their obstetrician respondent counterparts. This could be explained by the fact that the study was anesthesiology led, but other reasons could also be responsible.

In conclusion, this study demonstrates the lack of a unified approach to first- and second-line uterotonic usage. It reveals a 'snapshot' of Canadian practice and needs to be interpreted in this light. An evidence-based approach to uterotonic usage, as well as the consensus of obstetricians and anesthesiologists, is warranted in order to improve the management of PPH due to uterine atony. Considering the variation in practice between-hospitals and between-subspecialists within each institution, institutional audits and standardization of care for prophylaxis and treatment of uterine atony are necessary. The use of consistent, evidence-based societal guidelines can help to bring uniformity to clinical practice. More research may be needed to provide further evidence before change to national guidelines.

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Competing interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijoa.2018.09.002.