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Comparative analysis of antidiuretic effects of oxytocin and carbetocin in postpartum hemorrhage prophylaxis: a retrospective cohort study

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Abstract

Objectives: To compare the antidiuretic effects of oxytocin and carbetocin in patients undergoing elective caesarean section.

Methods: This retrospective cohort study included 276 participants who underwent elective singleton caesarean sections, with 184 receiving oxytocin and 92 receiving carbetocin. Exclusion criteria comprised patients with additional medical conditions or drug use affecting urine output, those diagnosed with postpartum hemorrhage, and those requiring non-standard intravenous fluid administration or additional uterotonics. Data on demographic characteristics, urinary output, time to reach specific urine output thresholds (500 mL, 1,000 mL, and 1,500 mL), vital signs, and hemoglobin levels were collected and compared between the oxytocin and carbetocin groups.

Results: There were no significant differences in demographic characteristics between the groups. There were no significant differences in preoperative and postoperative hemoglobin levels, vital signs or duration of hospitalization between the two groups. The carbetocin group exhibited significantly higher total urine output in the first 6 h

compared to the oxytocin group ($p=0.037$). The time required to achieve urine output volumes of 500, 1,000, and 1,500 mL did not differ significantly between groups.

Conclusions: Carbetocin may exert a less pronounced antidiuretic effect than oxytocin following elective caesarean section in a cohort with as few confounding factors as possible. Further prospective studies are warranted to validate these findings and assess their clinical implications in postpartum hemorrhage prophylaxis.

Keywords: carbetocin; oxytocin; diuresis; caesarean section; uterotonics

Introduction

Postpartum hemorrhage (PPH) is defined as blood loss of 1,000 mL or more within the first 24 h after childbirth, or any amount of blood loss that leads to signs and symptoms of hypovolemia [1]. PPH is a significant contributor to maternal morbidity and mortality, requiring prompt medical attention to avoid severe complications. Uterotonics play a crucial role and are broadly recommended in prevention and management of PPH by promoting uterine contractions to reduce bleeding [2]. World Health Organization (WHO) recommends active management of the third stage of the labour to avoid postpartum haemorrhage [2]. Oxytocin, ergometrin, misoprostol and carbetocin are uterotonics take place in the Essential Medicines List by the WHO [3, 4].

Oxytocin is a recommended and commonly used uterotonic which works on receptors of smooth muscle and stimulate the upper uterine segment to contract regularly but it can cause several adverse effects, including nausea, vomiting and headaches. Among these, one of the more concerning effects is its antidiuretic action, which arises from oxytocin's structural similarity to vasopressin. This similarity allows oxytocin to bind to vasopressin receptors in the kidneys, leading to increased water reabsorption and reduced urine output [5]. In severe cases, this antidiuretic effect can result in water intoxication, characterized by

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symptoms such as confusion, hyponatremia, seizures, or even coma [5–9].

Carbetocin is another alternative for prevention of PPH which is a long-acting synthetic oxytocin analogue works by stimulating the uterus [3, 10]. It has been shown in animal experiments that carbetocin and its metabolites, by binding to vasopressor receptors, cause antidiuresis as oxytocin does [11].

While some studies comparing carbetocin and oxytocin in many different aspects have shown no significant differences in terms of efficacy in preventing postpartum haemorrhage, the need for additional uterotonics and some side effects [3, 10, 12]; some others consider carbetocin as a comparable alternative to oxytocin regarding some of these effects [13, 14]. Besides those, there are very few clinical studies comparing carbetocin with oxytocin in terms of diuresis but only as secondary outcomes. Studies compared these two uterotonic agents regarding their effects to diuresis – due to their designs which are not only aiming to compare this outcome – had limits in terms of the results due to the differences of other confounding factors like blood loss, changes in haemoglobin levels and need for additional uterotonics effecting the diuresis between groups [15–19].

In this study, we aimed to contribute to the literature as the first ever study primarily aiming to compare oxytocin and carbetocin in terms of their antidiuretic effects via evaluating the hourly urine outputs of participants and making a comparison between two groups in this regard.

Materials and methods

The women included in the study were selected among individuals who had a term singleton delivery by an elective caesarean section with regional anaesthesia in Hacettepe University Faculty of Medicine, Department of Obstetrics and Gynaecology. We excluded patients with a trial of labour or who attended the delivery room in the active stage of labour. To avoid possible confounding factors as far as possible, we also excluded patients with additional medical condition including renal problems or hypertensive disorders such as preeclampsia and drug use that would affect urine output in their history. Any patient diagnosed as postpartum hemorrhage or required additional uterotonic agents or surgical interventions were also not included in this study. All caesarean section deliveries' intraoperative and postoperative care in terms of intravenous fluid administration procedures and analgesics were standard. Cases with need of excess fluid replacement rather than standard due to any reasons were excluded from the study.

We included 184 and 92 patients who were applied 10 International Units (IU) of Synthetic Oxytocin in intravenous fluid (oxytocin group) or 100 µg carbetocin in intravenous fluid (carbetocin group), respectively. The uterotonics were administered immediately following the removal of the placenta. The choice of uterotonic agent was determined by the primary obstetrician. Urinary output follow-up was initiated after the completion of surgery. Our clinical approach during the intraoperative and postoperative period was standard throughout the study period. The routine standard intraoperative and postoperative intravenous fluid regimen was administration of Ringer's Lactate solution 125 cc per hour until the 24th h postoperative. As analgesic, routine standard approach was to administer iv 100 mL of 10 mg/mL Paracetamol every 12 h. Until 6th postoperative hour, oral intake was ceased in all participants until successful mobilisation. Urinary catheters were removed when patients achieved a urine output of 1,500 mL according to our clinical follow-up algorithms. Patients who required any medical intervention or intravenous fluid other than these standard and routine applications were not included in this study cohort.

Retrospectively, age, obstetric history, maternal weight and height, gestational week and birth weight at delivery, duration of hospitalisation, vital signs at the 2nd, 4th and 6th h after delivery, haemoglobin values in g/dL before and after delivery, time to reach 500, 1,000 and 1,500 cc urine output after delivery and urine output at the 6th h postpartum were noted for all women included in the study and compared between oxytocin and carbetocin used groups. Blood pressures and heart rates (categorized as bradyrhythmic, normorhythmic and tachyrhythmic) were also recorded and compared between groups.

The study protocol was approved by the Hacettepe University Health Sciences Research Ethics Committee (SBA 23/052).

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS.22, IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.). To ensure the appropriate statistical tests for analyzing our data, we conducted an assessment of normality across our variables. Normality checks were performed using visual methods, such as histograms and Q-Q plots, alongside statistical tests like the Kolmogorov-Smirnov test. Due to a lack of normal distribution, the quantitative variables were given as median values and minimum-maximum. We have performed Mann-Whitney U test for comparing groups with continuous variables. Categorical variables were also compared by Chi-square test. Additionally, we conducted multiple linear regression analysis to examine the potential relationship between various contributing factors and urine output. A p-value of <0.05 was regarded as statistically significant.

Results

The 276 participants' median maternal age was 29 years, the median maternal BMI was 28.9 and the median gestational week at delivery was 38 (37–40). For urine output, the median durations to reach 500 mL, 1,000 mL, and 1,500 mL were 3 h, 6 h and 8.75 h respectively in whole cohort. The median total urine output for the first 6 h was 1,000 mL (150–3,300 mL). Additionally, the median preoperative hemoglobin (Hb) level was 12.1 g/dL, while the median postoperative Hb level was 10.5 g/dL. The demographic and clinical characteristics of the participants are shown in Table 1.

Comparing the oxytocin and carbetocin groups, there were no significant differences observed in maternal age, gravidity, maternal BMI or gestational week at delivery between the two groups. Despite having same median, minimum, maximum values, parity has been shown to be significantly different between groups ($p = 0.02$). To further elucidate this finding, we presented the distribution of parities in each study arm and conducted statistical analyses, which resulted in no significant difference between the groups. Regarding clinical outcomes, there was no statistically significant difference in the duration of hospitalization between the oxytocin and carbetocin groups. Similarly, no significant differences were observed in the duration of urine output to reach 500 mL, 1,000 mL, and 1,500 mL, nor in the median preoperative and postoperative hemoglobin levels between the two groups. However, the urine output for the first 6 h postpartum was significantly higher in the carbetocin group (1,067.5 mL) compared to the oxytocin group (925 mL) ($p = 0.037$) (Table 2). Vital signs at the 2nd, 4th,

Table 1: Demographic and some clinical characteristics of the participants.

	Median (minimum – maximum)
Maternal age	29 (18–43)
Gravidity	1 (1–7)
Parity	0 (0–3)
Maternal BMI	28.9 (18.7–43.4)
Gestational week	38 (37–40)
Birthweight	3,160 (2,040–4,210)
Duration of hospitalization, days	2 (1–7)
Duration (hours) of urine output for	
500 mL	3 (0.5–10)
1,000 mL	6 (1–16)
1,500 mL	8.75 (3–20)
Urine output for the first 6 h, mL	1,000 (150–3,300)
Preoperative Hb, g/dL	12.1 (8.1–16.0)
Postoperative Hb, g/dL	10.5 (6.0–13.9)

Continuous variables are presented as median (minimum-maximum).

Table 2: Comparison of demographic information and urine outputs of participants received oxytocin and carbetocin.

	Oxytocin	Carbetocin	p-Value
Maternal age, years	29 (18–41)	29 (18–43)	0.898
Gravidity	1 (1–4)	2 (1–7)	0.371
Parity	0 (0–3)	0 (0–3)	0.020
Number of parities			
0	124 (67.3 %)	48 (52.1 %)	0.091
1	45 (24.4 %)	31 (33.6 %)	
2	12 (6.5 %)	11 (11.9 %)	
3	3 (1.6 %)	2 (2.1 %)	
Maternal BMI, kg/m ²	29.0 (18.7–42.9)	28.5 (21.6–43.4)	0.250
Gestational week	38 (37–40)	38 (37–40)	0.050
Birthweight	3,210 (2,380–4,210)	3,015 (2,040–4,140)	0.030
Duration of hospitalization, days	2 (1–7)	2 (1–6)	0.807
Duration (hours) of urine output for			
500 mL	3.25 (1–9)	2.75 (0.5–10)	0.216
1,000 mL	6 (2–15)	5.5 (1–16)	0.249
1,500 mL	8.75 (3–20)	8.75 (3–18)	0.898
Urine output for the first 6 h, mL	925 (150–2,700)	1,067.5 (240–3,300)	0.037
Preoperative Hb, g/dL	12.2 (8.1–16)	12.1 (9.1–14.3)	0.702
Postoperative Hb, g/dL	10.5 (6–13.9)	10.5 (7.3–13.6)	0.701

p-Values with statistically significant differences are written in bold.

and 6th h postpartum showed no significant differences in heart rate, systolic blood pressure, or diastolic blood pressure between the oxytocin and carbetocin groups (Table 3).

We conducted a multiple linear regression analysis to evaluate factors influencing urine output at the 6th postoperative hour. The model included parity, gestational age, birthweight, and choice of uterotonic agent as potential contributing factors (Table 4). Our analysis demonstrated a significant inverse relationship between birthweight and urine output at the 6th postoperative hour, indicating that higher birthweights were associated with reduced urine output in this timeframe.

Discussion

Oxytocin and carbetocin are widely studied in the current literature in terms of their uterotonic effect and their clinical efficacy in postpartum haemorrhage prophylaxis [14, 17, 20]. However, there are only a few studies in the current literature comparing the antidiuretic effects of oxytocin and carbetocin. The antidiuretic effect of oxytocin and its molecular mechanisms have been demonstrated in the literature for at

Table 3: Comparison of vital signs of participants received oxytocin and carbetocin.

	Oxytocin (n=184)	Carbetocin (n=92)	p-Value
Vital signs at 2nd hour			
Heart rate			0.443
Bradycardic	1 (0.5 %)	2 (2.1 %)	
Normocardic	180 (97.8 %)	88 (95.8 %)	
Tachycardic	3 (1.6 %)	2 (2.1 %)	
Systolic blood pressure, mmHg	110 (90–150)	110 (90–130)	0.895
Diastolic blood pressure, mmHg	70 (52–98)	70 (60–92)	0.881
Vital signs at 4th hour			
Heart rate			0.179
Bradycardic	1 (0.5 %)	1 (1.1 %)	
Normocardic	182 (98.9 %)	88 (95.8 %)	
Tachycardic	1 (0.5 %)	3 (3.2 %)	
Systolic blood pressure, mmHg	110 (80–144)	110 (90–150)	0.748
Diastolic blood pressure, mmHg	67.5 (50–100)	65 (50–82)	0.898
Vital signs at 6th hour			
Heart rate			0.358
Bradycardic	0	1 (1.1 %)	
Normocardic	177 (96.1 %)	88 (95.8 %)	
Tachycardic	7 (3.8 %)	3 (3.2 %)	
Systolic blood pressure, mmHg	110 (90–150)	110 (90–150)	0.658
Diastolic blood pressure, mmHg	70 (50–100)	70 (50–100)	0.799

Table 4: Multiple linear regression analyses for the urine output at 6 h.

Model	Unstandardized coefficients		Standardized coefficients	T	p-Value
	B	Standard error	Beta		
Constant	1295.511	1257.971		1.030	0.304
Parity	36.596	37.000	0.062	0.989	0.324
Birthweight	−6.769	2.111	−0.191	−3.206	0.002
Gestational week at delivery	6.755	32.648	0.013	0.207	0.836
Uterotonic agent	−72.043	55.073	−0.079	−1.308	0.192

p-Values with statistically significant differences were written in bold.

least 60 years [5–7, 21]. Carbetocin's antidiuretic effect is also mentioned in the literature [11]. The majority of the clinical studies had investigated the potential antidiuretic effects of these agents as a secondary outcome, rather than focusing on this specific issue. To date, our study represents the first research filling this gap in the literature by excluding potential confounding factors as far as possible and focusing on a direct comparison of these agents in terms of antidiuretic effect.

In our study, carbetocin and oxytocin groups were composed of 92 and 184 women respectively. We did not include those who needed additional uterotonic, those who were diagnosed with postpartum haemorrhage, even if managed medically or by any other method, and those who needed additional administration of intravenous fluids in non-standard amounts in postpartum management. Our study revealed no significant difference between groups regarding the preoperative and postoperative haemoglobin values, systolic and diastolic blood pressure, heart rate in the postoperative 2nd, 4th and 6th h.

In our study, total diuresis of the participants included in the carbetocin group were significantly higher than the oxytocin group in the first 6 h. There were no statistically significant differences in terms of the time to reach 500, 1,000 and 1,500 mL of urine output. Nevertheless, these values were also consistent with the finding that carbetocin group had a higher urinary output and we observed that the carbetocin group had a shorter time interval for reaching urinary outputs of 500, 1,000 and 1,500 mL compared to the oxytocin group. This finding may pose great clinical importance in cases like preeclampsia where the urinary output is clinically important. According to our findings, carbetocin may be the primary choice as an uterotonic agent in these patient groups to increase the urinary output. This may be translated into future clinical implications in clinical practice, taking post-surgical urine output monitoring into account, which is also an important indicator of haemodynamic stability. Our multiple linear regression analyses revealed that birthweight significantly contributed to our findings, specifically showing an inverse relationship with urine output at the 6th postoperative hour. This observation underscores the importance of considering birthweight as a potential factor influencing postoperative urine output when interpreting our results. While this finding adds an intriguing dimension to our study, it also highlights the need for caution in drawing clinical conclusions. Further research with larger cohorts and a prospective design is necessary to validate this relationship and determine whether it translates to a clinically relevant outcome. Such studies could substantiate the potential utility of birthweight as a factor in postoperative management and help clarify its practical application in clinical settings.

There are very few clinical studies comparing carbetocin with oxytocin in terms of antidiuretic effects, but not as primary outcomes [15–19]. According to one study conducted by De Bonis et al., carbetocin had a lesser antidiuretic hormone effect regarding the 24-h urinary output without statistical significance [15]. However, another study Arunshankar et al.

demonstrated statistical significance consistence with the results of the previously mentioned study [16]. Another prospective study aimed to compare the haemodynamic effects of oxytocin (n=51) and carbetocin (n=51) and to assess the efficacy of these two drugs in terms of blood loss and the additional uterotonic needed in caesarean section at high risk of primary postpartum haemorrhage published by Larciprete et al. A further investigation was conducted in terms of urinary outputs as a secondary outcome. This revealed that the carbetocin group exhibited a higher diuresis than the oxytocin group at both 2 and 12 h after caesarean section. However, the difference was statistically significant only for the comparison at the 12-h postoperative period. [17]. A retrospective study aiming to compare the haemodynamic effects of two agents in preventing postpartum haemorrhage between the carbetocin group composed of 42 women and oxytocin group composed of 78 revealed lower rate of blood loss ≥ 500 mL and a statistically significant less time to reach the level of postoperative 1,500 mL of urine in the carbetocin group [18]. However, interpreting this result is challenging as there are significant differences between groups in terms of blood loss which also directly affects the urinary output. All of these studies show a higher urinary output in favour of carbetocin. Other studies compare oxytocin and carbetocin group in terms of diuresis revealed no significant differences in this regard [19, 22]. However, all of these studies are designed to compare the uterotonic affect of carbetocin with oxytocin. Thus, many confounding factors exist in these cohorts. In our study, our primary was to compare the urinary outputs for carbetocin and oxytocin groups. Therefore, we used strict inclusion and exclusion criteria to minimize the differences in other factors that may affect urine output. All participants received the same standardized volume of intravenous fluids. Any deviations, such as additional fluid requirements, were criteria for exclusion to minimize confounding factors. We think that our results pose a great importance as this is one of the first studies focusing on the comparison of two widely used uterotonic agents in terms of urinary output. We aimed to exclude any potential confounders as far as possible and made our analyses and created our cohort accordingly. Our main finding showing that significant difference in the urinary output at 6th h. This finding may be clinically important especially in patients where the urinary output is critical. With the approvement of our findings with further prospective studies, we may be offering carbetocin as a first choice of drug in patients like preeclampsia or diabetes mellitus.

We believe our findings hold considerable importance, as this is one of the first studies to directly compare two widely used uterotonic agents with respect to their impact on urinary output. Our study was designed to minimize the

influence of potential confounders, and we carefully structured our cohort and analysis methods to mitigate these factors to the extent possible. Our primary result – a significant difference in urinary output at the 6th postoperative hour – suggests a potentially meaningful clinical effect, especially for patients in whom urinary output is a critical factor in postoperative care. This finding may have particular relevance for populations with conditions such as preeclampsia or diabetes mellitus, where urinary output is closely monitored and managed as an essential marker of renal and overall health. If confirmed by further prospective research, our results could support the consideration of carbetocin as a preferred uterotonic agent in these high-risk groups, providing clinicians with evidence to guide therapeutic decisions more effectively. Future studies in larger and diverse cohorts would be valuable in substantiating these initial findings and exploring the broader clinical implications for optimizing postoperative care in specific patient populations.

Major limitation of this study is its retrospective design. However, we used strict inclusion and exclusion criteria to avoid confounding factors as far as possible in our analyses. On the other hand, the design of our study, which allows us to evaluate the effects of these two uterotonic agents used in postpartum hemorrhage prophylaxis after elective caesarean section only on diuresis by minimizing differences due to other factors that may affect diuresis, will be the first study in the literature that primarily aims to investigate the effect of these two groups on diuresis.

In conclusion, we showed that carbetocin exerts a less pronounced antidiuretic effect than oxytocin. However, our results should be confirmed and clinical importance of this issue should be questioned by further prospective studies.

Research ethics: The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by Hacettepe University Health Sciences Research Ethics Committee (SBA 23/052).

Informed consent: Not applicable.

Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission. U Kayıkçı: Protocol/Project Development, Data Collection, Manuscript Writing/Editing. E Fadiloğlu: Protocol/Project Development, Data Analysis, Manuscript Writing/Editing. AÇ Bayrak: Data Collection, Data Analysis. EA Kır: Data Collection. İ Hergüner: Data Collection. K İskandarlı: Data Collection. Ö Deren: Protocol/Project Development, Data Analysis, Manuscript Writing/Editing.

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