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A randomized controlled trial of methylergonovine prophylaxis after dilation and evacuation abortion ☆,☆☆,★

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ABSTRACT

Objective: To evaluate the efficacy of intramuscular methylergonovine maleate as prophylaxis against excessive bleeding when given after dilation and evacuation (D&E) at 20–24 weeks.
Study design: We performed a randomized, double-blinded, placebo-controlled trial in patients without excessive bleeding requiring intervention after D&E completion. We administered study treatment within one minute of the end of the procedure. We primarily compared outcomes using a composite of indicators of excessive post-procedure blood loss (post-procedure measured blood loss exceeding 125 mL, uterine massage or compression for at least two minutes, administration of additional uterotonic medication, intrauterine balloon tamponade, uterine re-aspiration, blood transfusion, uterine artery embolization, hospital admission for bleeding, or major surgery). Secondary outcomes included individual indicator occurrences, satisfaction, and side effects.
Results: From March 3, 2015 to March 31, 2017, we randomized 284 participants ($n = 140$ methylergonovine, $n = 144$ placebo), five before we registered the trial with clinicaltrials.gov. Baseline characteristics were similar between groups. The composite outcome occurred in 78 (56%) methylergonovine and 75 (52%) placebo participants ($p = 0.5$). Methylergonovine recipients required more intrauterine balloon use ($n = 20$ [14%]) versus placebo ($n = 10$ [7%]), $p = 0.04$. We also observed a non-significant trend towards more uterotonic administration ($n = 56$ [40%] versus $n = 43$ [30%], $p = 0.07$) and hospital admissions for bleeding ($n = 4$ [3%] versus $n = 0$, $p = 0.06$) in the methylergonovine group compared to placebo.
Conclusion: We observed no improvement in the composite outcome for excessive bleeding with prophylactic post-procedure methylergonovine. In addition, individual excessive bleeding outcomes occurred more frequently in the methylergonovine group, potentially indicating harm with its prophylactic use after D&E.
Implications: When administered prophylactically immediately after dilation and evacuation abortion at 20–24 weeks, methylergonovine increases uterine bleeding. Given the lack of data for effectiveness as a prophylactic agent and our findings indicating harm, we do not recommend its use for post-operative prophylaxis.

1. Introduction

Clinically significant hemorrhage after routine D&E is infrequent, with studies reporting an incidence of 0.9–10 per 1000 [1–3]. Defintions of hemorrhage vary with some studies using blood loss and other studies using specific interventions like transfusion, admission or other procedures [1]. No studies have described the incidence of excessive bleeding. Measures used by providers to decrease or control excessive bleeding after D&E

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include balloon tamponade, fundal massage, and of uterotonic administration [4].

Most D&Es are performed in an outpatient setting, about half of which have no immediate access to higher level care [4]. In addition, because of the lack of providers in many counties, women travel great distances to access D&E and have limited ability to follow up with an experienced provider for complications [5]. Because of the landscape in which D&Es are provided, many providers are highly motivated to prevent any concerning bleeding before discharging patients home.

About one-quarter of D&E providers report routinely using uterotonics before or after procedures over 20 weeks gestation. Methylergonovine is used most commonly, by almost two-thirds of D&E providers [4]. Methylergonovine, a first-line agent in treating post-abortion hemorrhage [1] is an ergot alkaloid with vasospastic and smooth muscle contractile effects [6]. One low-quality study provides evidence that methylergonovine may be associated with fewer first-trimester abortion complications [7]. While there is evidence to guide abortion providers in identifying women at risk of hemorrhage, there is little evidence to guide practice with prevention of bleeding, specifically regarding use of prophylactic uterotonic medications. Given the widespread use of prophylactic methylergonovine without evidence for benefit in preventing excessive bleeding from D&E, we sought to evaluate its effectiveness as a prophylactic agent.

2. Material and methods

We conducted a randomized, double-blinded, placebo-controlled trial of methylergonovine versus placebo after D&E at 20–24 weeks. We recruited patients from March 3, 2015 to March 31, 2017 from a hospital-based, outpatient abortion clinic, five of whom we randomized before registration with clinicaltrials.gov (NCT02408965) on March 11, 2015. In preparation for the study, we measured post-D&E blood loss among 25 consecutive patients within this gestational range to define expected post-procedural blood loss. Blood loss ranged from 25 to 170 mL with 95% of patients less than 125 mL; therefore, we used 125 mL as an indicator of excessive bleeding for our study.

Eligible patients were women ages 18 and older who were between 20 weeks 0 days and 24 weeks 0 days dated by ultrasonography, and who spoke English or Spanish. Exclusion criteria were hypertension on the preoperative or operative day (defined as systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg), D&E procedures with more than one day of cervical preparation with dilators, use of protease inhibitors, known coagulopathy, or known or suspected morbidly adherent placenta.

A research assistant not involved in the study generated a random sequence of numbers from a computer-generated randomization scheme in a 1:1 fashion. We use block randomization in blocks of 10 stratified by two gestational groups, 20 weeks 0 days to 21 weeks 6 days and 22 weeks 0 days to 24 weeks 0 days. The list was electronically delivered to the inpatient pharmacy where pharmacists prepared and dispensed blinded study drugs to research staff. Pharmacists prepared sequentially numbered syringes of methylergonovine maleate 0.2 mg or saline placebo as 1 mL in a 3 mL syringe, and labeled as study drug. All clinic staff, research staff, D&E providers, and study participants remained blinded to the study drug assignment.

We consented participants after ultrasound examination, counseling, and consent for the abortion, and before osmotic dilator placement at the pre-operative visit (day 1). On the procedure day (day 2), experienced physicians, including attendings and second-year family planning fellows, did all D&E procedures. The standard D&E procedure included a paracervical block of chloroprocaine 1% 20 mL with vasopressin 4 units, mechanical cervical dilation if necessary, amniotic fluid evacuation with suction, forceps evacuation of fetal parts, then placenta, sharp curettage, and final suction. Most patients over 20 weeks in our hospital-based clinic receive anesthesiologist-administered deep sedation with Propofol, with the remainder receiving nurse-administered moderate sedation with fentanyl and midazolam.

At the end of the D&E, defined as the end of final suction, we assessed participants' bleeding and blood pressure. We enrolled (provided study treatment) to participants not requiring treatment for active bleeding and without elevated blood pressure. Within one minute of the end of the procedure, a nurse administered the next sequential study drug intramuscularly in the participant's right thigh. Treating physicians were allowed to administer additional uterotonics after study drug administration at their discretion. Participants recovered for approximately one hour after the D&E, consistent with clinic standard of care. We measured post-procedure blood loss in the recovery room by weighing pads and linens in addition to a semi-quantitative assessment of blood loss in the toilet.

We collected baseline demographics, gestational duration, obstetric and medical histories, cervical preparation method (number of osmotic dilators and adjunctive medications used), baseline blood pressure, anesthesia type, need for mechanical cervical dilation, length of D&E procedure, difficulty of procedure (reported by the D&E provider as a 4-point Likert scale), and procedural measured blood loss [8].

Our primary outcome was a composite of post-procedure excessive bleeding indicators. This composite outcome included post-procedure blood loss greater than 125 mL, uterine massage or compression for at least two minutes, administration of additional uterotonic medication, intrauterine balloon tamponade, uterine re-aspiration, blood transfusion, uterine artery embolization, hospital admission for bleeding, or major surgery. Any one indicator met criteria for excessive bleeding. Secondary outcomes included each individual outcome in the composite, total number of interventions for excessive bleeding per participant, provider and nurse satisfaction with post-abortion bleeding, and participant side effects after study drug injection.

To estimate sample size, we first reviewed our own database of cases at 20–24 weeks from September–December 2014; among 162 cases, we found that 35% met criteria for the composite outcome. We assumed a 15% reduction of excessive bleeding in the methylergonovine group (20%) versus placebo (35%), consistent with another study evaluating interventions for bleeding at the time of D&E that used a 15% reduction as the basis for sample size [9]. We estimated 284 patients would be needed using a two-sided alpha of 0.05 and 80% power.

A data safety monitoring board reviewed interim results after we enrolled one-third of participants. Their criteria for stopping included any serious bleeding outcomes that were statistically significantly different between groups. We used an intent-to-treat analysis and conducted the statistical analysis in blinded fashion. We evaluated demographic characteristics and secondary outcomes using chi-square and Fisher's exact tests as appropriate for categorical variables, as well as *t*-tests and Kruskall–Wallis tests for continuous variables, depending on normality of distribution. We calculated relative risks and 95% confidence intervals for the primary composite outcome to compare methylergonovine and placebo groups both in the overall study population and gestational subgroups. We did sensitivity analyses excluding the outcome of uterine massage and compression as criteria for the composite outcome to evaluate any effect of the study drug on more invasive interventions for excessive bleeding. We considered *p*-values less than 0.05 to be statistically significant. We performed

all statistical analyses using Stata version 14.1 (College Station, TX USA). Subejcts were compensated for participation. The study was approved by the University of California, San Francisco (UCSF) Committee on Human Research.

Clinical Trial Registration: ClinicalTrials.gov, registration number NCT02408965.

3. Results

During the study period, we assessed 1384 subjects for eligibility. We consented 320 subjects and enrolled 284 (Fig. 1). Only 14 (4.4%) consented subjects had significant bleeding at the end of the procedure which excluded enrollment. Subject characteristics are presented in Table 1. While mean intraoperative blood loss was similar between groups, the methylergonovine group had a higher proportion of cases with intraoperative blood loss greater than 90% of the mean ($n = 28$ [20%] versus $n = 13$ [9%], $p = 0.03$).

Table 2 demonstrates bleeding outcomes with study treatment. The composite outcome of excessive bleeding occurred in 78 (56%) of the methylergonovine group and 75 (52%) of the placebo group. Our sensitivity analysis did not show any difference when we excluded massage or compression from the composite outcome. Because intraoperative blood loss greater than 90th percentile of the mean was different between groups, we did an additional analysis controlling for intraoperative blood loss; the association between the intervention and the composite outcome was unchanged. The methylergonovine group had significantly more use of intrauterine balloon tamponade compared to placebo ($n = 20$ [14%] versus $n = 10$ [7%], $p = 0.04$) and a trend towards more frequent administration of at least one uterotonic medication ($n = 56$ [40%] versus 43 [30%], $p = 0.07$). In addition, the methylergonovine group experienced more admissions for bleeding ($n = 4$ [3%] versus $n = 0$, $p = 0.05$). Two subjects underwent uterine artery embolization, both in the methylergonovine group. The mean

Table 1
Demographic and procedural characteristics of women randomized to post-operative prophylactic intramuscular methylergonovine or placebo for dilation and evacuation abortion at 20–24 weeks.

	Methylergonovine $n = 140$	Placebo $n = 144$	p-value
Age	24.5 (21–29)	25 (21–31)	0.6
Race/Ethnicity			0.7
Non-Hispanic White	39 (28)	48 (33)	
Non-Hispanic Black	26 (19)	33 (23)	
Hispanic	37 (27)	33 (23)	
Asian	7 (5)	7 (5)	
Multiracial	19 (13)	15 (10)	
Other	11 (8)	8 (6)	
Body mass index	26.5 (23–31)	26 (23–29)	0.3
Nulliparous	35 (25)	37 (26)	0.9
Prior cesarean section	24 (17)	27 (19)	0.7
Current or recent cocaine or methamphetamine use	11 (8)	19 (13)	0.1
History of bleeding disorder[a]	2 (1)	3 (2)	0.7
Gestation, weeks	21.6 (21–23)	21.5 (20–23)	0.4
Cervical preparation[b]			0.6
Dilators only	106 (76)	108 (75)	
Dilators + mifepristone	33 (24)	35 (24)	
Dilators + misoprostol	0 (0)	1 (1)	
Needed mechanical dilation	7 (5)	5 (3)	0.5
Procedural anesthesia			0.8
Deep sedation	125 (89)	125 (87)	
Moderate sedation	13 (10)	17 (12)	
General anesthesia	2 (1)	2 (1)	
Length of procedure, minutes	12 (8–16)	12 (9–15)	0.4
Procedural measured blood loss	300 (150–400)	250 (150–425)	0.8

All data presented as n (%) or median (interquartile range).
[a] Missing data, $n = 9$.
[b] Missing data, $n = 1$.

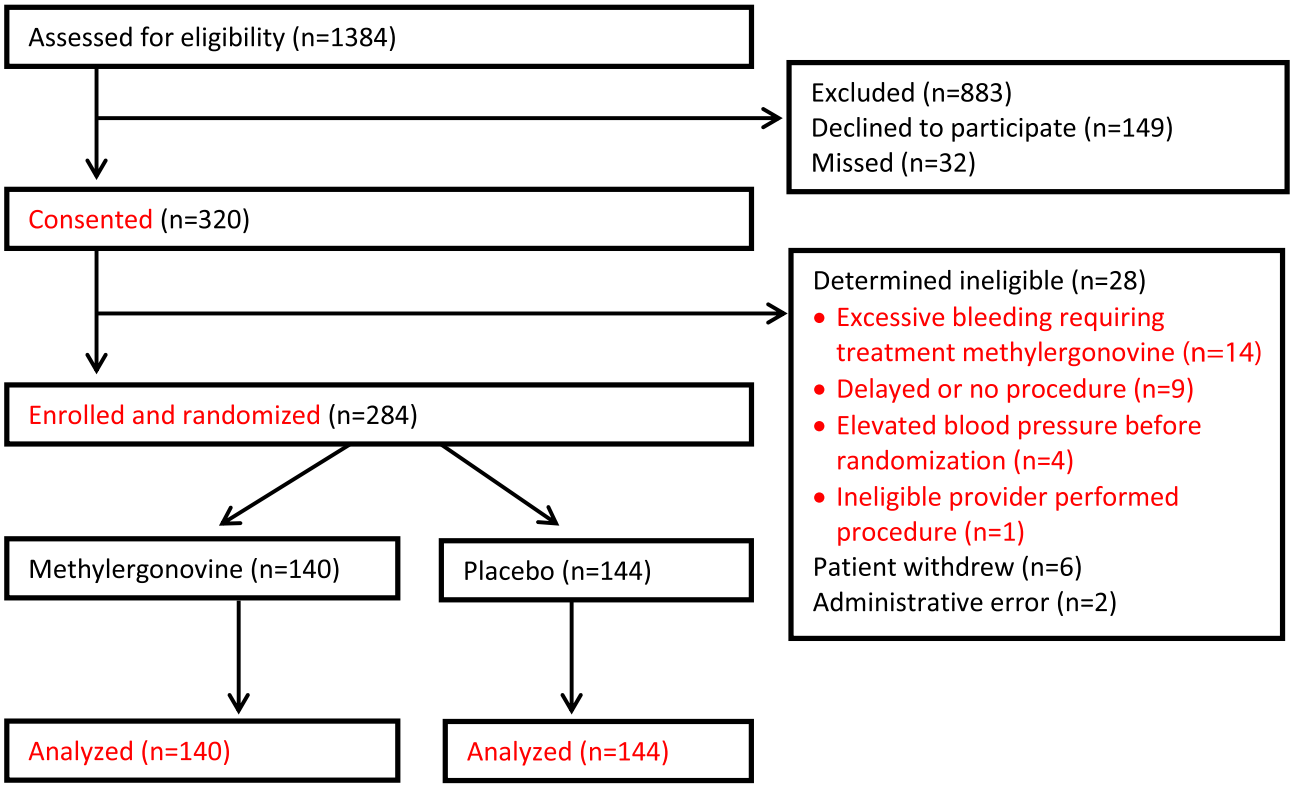

Fig. 1. Study flow of subjects randomized to post-operative prophylactic intramuscular methylergonovine or placebo for dilation and evacuation abortion at 20–24 weeks.

Table 2
Effect of post-operative prophylactic intramuscular methylergonovine versus placebo on excessive bleeding after dilation and evacuation abortion.

	Methylergonovine $n = 140$	Placebo $n = 144$	RR (95%CI)	p-value
Composite outcome[a]	78 (56)	75 (52)	1.1 (0.9–1.3)	0.5
Balloon tamponade	20 (14)	10 (7)	2.1 (1.0–4.2)	0.04
Post-procedure blood loss > 125 cc	32 (23)	23 (16)	1.4 (0.9–2.3)	0.1
Post-procedure blood loss	126 ± 241	76 ± 69	–	0.02
Massage/compression	51 (36)	46 (32)	1.1 (0.8–1.6)	0.4
Uterotonic given	56 (40)	43 (30)	1.3 (0.97–1.8)	0.07
Reaspiration	4 (2.9)	0	–	0.06
Admission for bleeding	4 (3)	0	–	0.06
Transfusion	3 (2)	0	–	0.1
Uterine artery embolization	2 (1)	0	–	0.2
Major surgery	0	0	–	–

All data presented as n (%) or mean ± standard deviation.
[a] Composite outcome includes post-procedure measured blood loss greater than 125 mL, uterine massage or compression for at least two minutes, administration of additional uterotonic medication, intrauterine balloon tamponade, uterine re-aspiration, blood transfusion, uterine artery embolization, hospital admission for bleeding, or major surgery.

number of excessive bleeding outcomes was higher in the methylergonovine group versus placebo (1.3 versus 0.9, $p = 0.008$). While the proportions of subjects who received additional uterotonics was not significantly different between groups, the mean number of uterotonics used was higher in the methylergonovine group versus placebo (0.9 versus 0.6, $p = 0.01$). We observed no differences between groups in time to first or second uterotonic administration.

Table 3 delineates bleeding outcome by gestational age. In the 22–24 week gestational duration group, methylergonovine was associated with more excessive bleeding outcomes, including increased use of intrauterine balloon tamponade ($n = 13$ [19%] versus $n = 5$ [7%], $p = 0.04$), and more frequent administration of additional uterotonic medication ($n = 33$ [47%] versus $n = 22$ [31%], $p = 0.04$).

Compared to placebo, participants randomized to methylergonovine reported more nausea ($n = 42$ [30%] versus $n = 29$ [12%], $p < 0.001$). We observed a trend towards increased vomiting ($n = 18$ [13%] versus $n = 9$ [6%], $p = 0.06$ and cramping pain ($n = 99$ [71%] versus $n = 86$ [58%], $p = 0.07$) in the methylergonovine group; however, most participants reported they were not significantly bothered by these side effects. Overall, subjects reported headache ($n = 37$ [13%]), shortness of breath ($n = 17$ [6%]), vision changes ($n = 10$ [3.5%]), and palpitations ($n = 3$ [1%]), with no differences between groups.

Satisfaction outcomes are presented in online Appendix 1. Physicians were less likely to report being satisfied with post-procedure bleeding in the methylergonovine group, both overall ($p = 0.03$) and in the 20–22 week gestational duration group ($p = 0.01$). Nurses' and subjects' satisfaction with bleeding were similar between groups, as was surgeon-rated procedure difficulty. Physicians correctly guessed group assignment in 8% of cases, nurses in 30% of cases, and subjects in 8% of cases.

4. Discussion

We found that methylergonovine, when given as a prophylactic medication immediately after D&E at 20–24 weeks, is associated with increased rather than decreased bleeding. Providers commonly use methylergonovine after D&E as a prophylactic medication in an attempt to prevent excessive bleeding; however, we demonstrated increased admissions for bleeding, increased use of balloon tamponade, and increased use of additional uterotonic medications to control bleeding. Physicians were less satisfied with post-D&E bleeding in patients who received prophylactic methylergonovine after D&E, and patients experienced more side effects.

Much of our understanding of the actions of methylergonovine comes from obstetric literature. Given our divergent findings, we question whether methylergonovine may have different actions on the uterus at 20–24 weeks than it does at term. Methylergonovine has vasoconstrictive, vasospastic, and uterine-specific smooth muscle contractile properties [10]. The uterine contractile effect decreases uteroplacental blood flow and closes open vasculature in the vacant postpartum placental bed, which results in a reduction in bleeding [11]. We hypothesize that the effects of methylergonovine may be modulated by the fewer number of

Table 3
Effect of post-operative prophylactic methylergonovine versus placebo on excessive bleeding after dilation and evacuation abortions, by gestational group.

	20–22 week gestational group			22–24 week gestational group		
	Methylergonovine $n = 70$	Placebo $n = 72$	RR (95% CI)	Methylergonovine $n = 70$	Placebo $n = 72$	RR (95% CI)
Composite outcome[a]	34 (48)	37 (51)	0.9 (0.7–1.3)	45 (64)	40 (55)	1.2 (0.8–1.5)
Balloon tamponade	7 (10)	5 (7)	1.4 (0.5–4.3)	13 (19)	5 (7)	2.7 (1.0–7.1)
Post-procedure blood loss >125 cc	14 (20)	12 (17)	1.2 (0.6–2.4)	19 (27)	12 (17)	1.6 (0.9–3.1)
Massage or compression	18 (26)	23 (32)	0.8 (0.5–1.3)	33 (47)	23 (32)	1.4 (1.0–2.2)
Uterotonic given	23 (33)	21 (29)	1.1 (0.7–1.8)	33 (47)	22 (31)	1.5 (1.0–2.4)
Reaspiration	1 (1)	1 (1)	–	3 (4)	0	–
Admission for bleeding	2 (3)	0	–	2 (3)	0	–
Transfusion	1 (1)	0	–	2 (3)	0	–
Uterine artery embolization	1 (1)	0	–	1 (1)	0	–

All data are presented as n (%).
[a] Composite outcome includes post-procedure measured blood loss greater than 125 mL, uterine massage or compression for at least two minutes, administration of additional uterotonic medication, intrauterine balloon tamponade, uterine re-aspiration, blood transfusion, uterine artery embolization, hospital admission for bleeding, or major surgery.

available serotonin receptors on the uterus that the medication targets, specifically of the $5HT_2$ subtype [12,13]. With fewer uterine receptors, methylergonovine's vasoconstrictive and vasospatic properties and subsequent increase in central venous blood pressure may overpower the reduction in uterine contractile activity. This unchecked vasoconstrictive and vasospastic activity on the open vasculature of a post-D&E placental bed along with an increase in central venous pressure may increase blood flow out of the open vasculature, thereby causing greater blood loss. Supporting this hypothesis, the trauma literature describes reduced blood loss by employing hypotensive resuscitation during hemorrhagic shock, whereby a patient's blood pressure is maintained at a level low enough to reduce bleeding, but high enough for perfusion [14]. Lastly, the vasoactive effects of methylergonovine may have an additive bleeding effect with the already dilated low-resistance uterine spiral arteries that have little smooth muscle [15].

The lack of benefit from methylergonovine after D&E in our trial may be related to the timing of administration – specifically immediately after placental removal which is the end of the D&E and not before placental removal. A systematic review of methylergonovine as a prophylactic medication for postpartum hemorrhage (PPH) found no effect on preventing PPH when administered after placental removal. Furthermore, a different systematic review found that methylergonovine was effective in decreasing PPH when it was given in the third stage of labor, before the placenta was removed [16]. We cannot determine from our study whether the effect of methylergonovine on post-D&E bleeding would be different had the drug been administered before placenta was removed.

Finally, we must consider that methylergonovine may act differently when administered prophylactically versus as a treatment intervention. Robust evidence demonstrates that methylergonovine is effective in obstetrics as both a prophylactic and treatment medication. By contrast, our study demonstrates that methylergonovine is harmful when used prophylactically after D&E. While we currently have no reason to believe that methylergonovine is harmful or ineffective as a treatment medication for post-D&E bleeding, the rationale for its use is based on obstetric literature and not from any abortion-specific studies.

The strengths of our study include a robust randomization and blinding scheme whereby clinicians, researchers and subjects were blinded to assignment. We had no loss to follow up. To our knowledge, this is the first study to examine the prophylactic effect of a commonly used medication after D&E, and our findings may change routine practice. Limitations include the timing of prophylactic methylergonovine at the time of D&E. Specifically, our study only evaluated its use after D&E completion. Our findings may not be applicable to cases with administation before D&E, or before the placenta is removed. Furthermore, our findings may not be applicable to the use of prophylactic methylergonovine much longer after D&E completion, such as in the recovery room or at home.

D&E providers commonly use prophylactic uterotonic medications after D&E to avoid excessive bleeding. When administered prophylactically as an intramuscular injection immediately after D&E at 20–24 weeks, methylergonovine actually causes harm in addition to side effects and should not be used. Studies evaluating the effect of other uterotonic agents are warranted to better guide D&E practices.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2020.10.009.

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