Original Article

Randomised Control Trial of Oral Morphine and Intramuscular Pethidine for Post-Caesarean Section Analgesia in South-Western Nigeria

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Abstract

Background: The search for the ideal analgesia following caesarean section remains elusive but opioids provide good postoperative analgesia. Intramuscular opioid induces pain at the site of injection and its repeated administration proved to be more demanding for caregivers. Oral opioids especially morphine have become increasingly accessible in our environment and may be more effective than the conventional parenteral opioids for postcaesarean analgesia. **Aim:** To compare the efficacy of multiple doses of 10 mg oral morphine with that of 50 mg intramuscular pethidine in treatment of postcaesarean pain among parturients in Abeokuta, Nigeria. **Patients, Materials and Methods:** The study was a randomised controlled trial among parturients who had elective caesarean section in Abeokuta between November 2019 and August 2020. A total of 136 consenting and eligible pregnant women were randomised into two groups. Group A received multiple doses of 10 mg oral morphine while Group B had multiple doses of 50 mg intramuscular pethidine. The summed pain intensity difference (SPID) of the two groups was calculated and compared using the Chi-square and $P < 0.05$ was statistically significant. **Results:** The mean ± standard deviation (SD) of SPID at rest for morphine group and pethidine group was 6.00 ± 76.25 and 8.51 ± 77.60, respectively ($t = -0.439$ $P = 0.662$); the mean ± SD of SPID on movement for morphine and pethidine group was 29.13 ± 75.25 and 25.52 ± 28.47 ($t = 0.139$, $P = 0.890$). The median maternal satisfaction reported was similar in both groups ($\chi^2 = 2.773$, $P = 0.4963$) and somnolence was experienced in 3.1% of parturients in morphine group. **Conclusion:** The efficacy and maternal satisfaction of oral morphine in the control of postcaesarean section pain was similar to that of intramuscular pethidine. Hence, oral morphine is an acceptable alternative to intramuscular pethidine in management of pain following Caesarean section.

Keywords: Analgesia, caesarean section, intramuscular, morphine, pethidine

Introduction

Adequate postoperative analgesia in the obstetric patient is crucial as they have different surgical recovery needs including breastfeeding and care of the newborn which can be impaired if analgesia is unsatisfactory.[1] The dramatic rise in the rate of caesarean deliveries in the last two decades has made postoperative pain management of patients a major medical and nursing challenge.[2] Good pain control encourages early ambulation thereby reducing the risk of thromboembolism that is increased in pregnancy.[3,4] A study observed that poorly managed acute postoperative pain can lead to persistent or chronic pain and may cause a three-fold increase in the risk of postpartum depression, affecting both maternal and neonatal health.[5-7]

The number of options in managing postcaesarean pain is large and the choice of the methods of pain control is determined by drug availability, institutional protocols, individual preferences, available resources, and financial considerations.[8] Opioid analgesics are the gold standard for treating moderate-to-severe pain.[9] However, barriers to opioid

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use abound in the developing world. Furthermore, concerns at government level over risks of addiction and abuse may be a deterrent as import restrictions can be overly stringent as the laws regarding prescription and dispensing of opioids can make it extremely difficult to get opioids to the patients.[9]

The commonly used routes of administration of postoperative analgesia include intravenous, intramuscular, intrathecal, subcutaneous, and oral. Intramuscular and subcutaneous opioids are affordable and easy to administer but requirement for repeated and painful injections, variable systemic absorption, delayed onset of action, and fluctuating plasma levels of the drug are the major setbacks.[10] Patient controlled intravenous analgesia is being used in advanced climes but, its use in our environment is limited by the ability of the patients to use it correctly, the cost of the device as well as availability.[3] The oral route has the advantage of ease of administration, low cost, high maternal acceptance, and fewer opioid-related adverse effects as compared with the parenteral route.[10]

Evidence supporting the use of oral opioids as primary analgesia in the first postoperative day is insufficient.[9] Although oral morphine has been shown to provide satisfactory analgesia, randomised trials are still lacking,[11] hence the journey to find the ideal route and agent is evolving. This study compared oral morphine and intramuscular pethidine in the postcaesarean section pain management in the hope of reducing cost and stress of nursing staff while avoiding the pain of multiple intramuscular injections as well.

Patients, Materials and Methods

The study was a single-blinded, randomised controlled trial done at the Federal Medical Centre, Abeokuta, South-Western Nigeria. Only the researcher was blinded because the patient can easily distinguished between oral and intramuscular interventions. Ethical clearance was obtained from the hospital ethics committee with approval number FMCA/243/HREC/03/2018/09 and written informed consent was obtained from the participants.

The sample size was calculated using the formula below.[12]

Sample size $n = \frac{2SD^2(Z_{\alpha/2} + Z_{\beta})^2}{d^2}$

n = size per group;

SD = mean standard deviation of summed pain intensity difference (SPID) of both comparison groups which was 16.73, gotten from pilot study.

$Z\alpha_{/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ (From Z table) at type I error of 5%

$Z\beta = Z_{0.10} = 1.282$ (From Z table) at 90% power.

d^2 = effect size = between mean values (from pilot study) = 31.80-21.60 = 10.20

Thus the sample size was:

$n = \frac{2(16.73)^2 + (1.96 + 1.282)^2}{10.20^2}$

$n = \frac{2 \times 279.89 \times 10.51}{104.04}$

$n = 56.55$

n~57

Adding a 15% attrition rate; 57/85 × 100 = 67.06

The sample size for the two groups was 2n = 2 × 68 = 136

A total of 136 patients were recruited.

A total of 136 eligible pregnant women with American Society of Anesthesiology physical status 1 or 2, aged 18 years and above admitted for elective caesarean section, under spinal anaesthesia, were recruited into the study. The exclusion criteria were; chronic pain condition, allergy or contraindication to morphine or pethidine, chronic use of narcotics or substance abuse, and preeclampsia or eclampsia. The participants were randomised into either arm of the study using simple randomisation procedure (computer generated random numbers). The caesarean sections were performed by experienced Senior Registrars and Consultants while following standards surgical techniques to allow for uniformity. The study drugs were prepared, packaged, and labelled by the hospital pharmacist. The intervention group (Group A) had oral morphine (Oramorph™ brand of Boehringer Ingelheim Ltd.) 10 mg every 4 h for 24 h while the control group (Group B) was administered intramuscular pethidine (Verpat™ brand of Verve Human Care Laboratories.) 50 mg every 4 h for 24 h being the drug used in our centre for postoperative pain relief. The first dose of analgesia was administered 1 h after surgery for both groups and every 4 h for 24 h for both groups. Pain score at rest was assessed and recorded before the initial analgesic dosing using the 11-point Numeric Rating Scale of 0–10 (where 0 = no pain and 10 = worst possible pain) and this was taken as 0 h. Pain scores at rest and on movement were then assessed and recorded every 8 h thereafter for 24 h. Rescue analgesia was provided for both groups of participants with 75 mg of intramuscular diclofenac on request. A pro forma was used to record the pain scores and the maternal satisfaction, with the analgesia, was scored at the end of 24 h using the visual analogue scale (VAS). The side effects (nausea, vomiting, pruritus, somnolence and respiratory distress) experienced were also recorded. Sociodemographic data (Age, parity, gestational age, religion, level of education, occupation and tribe) number of previous caesarean section, maternal weight, maternal height and body mass index (BMI) of the participants were also recorded. The SPID was calculated using the formula $SPID_{ti\text{-}ti+n} = \sum_{-ti}^{ti+n} (PID_i) \times (t_i + {}_1\text{-}t_i)$ where t_i is the scheduled assessment time and PID_i is the pain intensity difference score calculated at each postbaseline time point.[13]

Data generated were analysed using the Statistical Package for the Social Sciences (SPSS) package version 23.0 (IBM, Armonk, NY, USA). Results were presented using Flow diagram, Box-Whiskers plot. The categorical variables were analyzed using Chi-square, Fisher's exact while continuous

variable were analysed using Student's *t*-test as appropriate. Statistical significance was set at $P < 0.05$.

Results

A total of 136 participants were recruited for the study. Out of this, 127 participants with complete data were analysed, 9 participants including 4 from Group A and 5 in Group B pulled out of the study. Five participants withdrew consent during surgery (Group A, $n = 2$, Group B, $n = 3$) while 4 participants (Group A, $n = 2$, Group B, $n = 2$) withdrew consent within 4 h of the study citing nonsatisfaction with pain control as the reason. One hundred and twenty-seven patients with complete data were analysed. (Group A, $n = 64$ and Group B, $n = 63$) as shown in Figure 1.

Most women in this study were in the age group of 30–39 years for both groups. The age distribution in Group A was similar to Group B with no significant difference ($P = 0.070$). Similar to age group, there were no significant differences in distribution of other sociodemographic variables such as religion, occupation, education, and tribe in both groups. More nulliparas were in Group A than Group B, equal number of study participants in both study groups had no previous caesarean delivery; more had only one previous caesarean section compare with those who had 2 or 3 previous caesarean section in both groups. Previous caesarean delivery is a major indication for caesarean section followed by fetal macrosomia in both groups, as shown in Table 1.

Figure 2 shows the variation in pain intensity difference (PID) at rest with time in the two study groups. At 8 h, the mean PID was higher in Group B with wider range than Group A, observation at 16 h showed that there was increase in the mean PID in Group B which was higher than in Group A. At 24 h, the mean PIDs were almost the same for both groups.

Figure 3 showed the variation in PID on movement with time in the two study groups. At 8 h, the mean PID was lower in Group A with narrower range than Group B, the mean PID observed at 16 h in Group A was lower than the mean PID at 8-h and the same as Group B. At 24 h, the mean PIDs were similar for both groups and lower than PID at 16 h.

The mean PID of both groups at rest and on movement at various evaluation times during the study. It also shows the mean SPID of the two groups. At 8 h and 16 h, the mean PIDs at rest were lower in Group A than Group B, while the mean PID at rest at 24 h was slightly lower in Group B than Group A. On movement, the mean PIDs at 8 h, 16 h, and 24 h were lower in Group B than Group A. The mean PIDs at rest and movement decreased with increasing time, highest at 8 h and lowest at 24 h. There was no significant difference in the mean PID in both groups at 8 h, 16 h, and 24 h ($P > 0.05$). The mean SPID at rest was lower in Group A than Group B, but Group A had wider range of SPID than Group B. On movement, mean SPID was lower in Group B than Group A, but Group B had wider range of SPID than Group A. There was no statistically significant difference in the mean SPID in both groups at rest ($P = 0.855$) and on movement ($P = 0.803$), as shown in Table 2.

None of the participants in both groups experienced nausea, vomiting, pruritus, and respiratory distress while 2

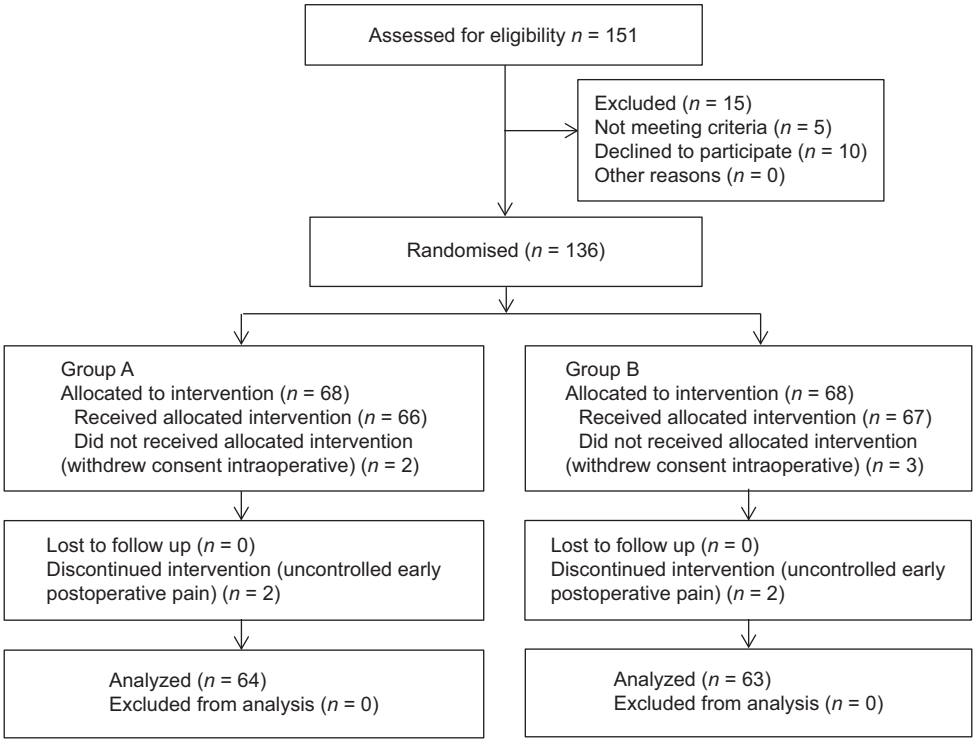

Figure 1: Flow chart of participants through the trial

Table 1: Sociodemographic and obstetric characteristics of participants in study groups

Variable	Group A: Morphine (*n*=64), *n* (%)	Group B: Pethidine (*n*=63), *n* (%)	χ^2/Fisher's exact/*t*-test	*P*
Age group (years)				
20-29	22 (34.4)	15 (23.8)	2.967[p]	0.255
30-39	39 (60.9)	41 (65.1)		
≥40	3 (4.7)	7 (11.1)		
Mean±SD	31.56±4.61	33.16±5.21	1.829[t]	0.070
Religion				
Islam	22 (34.4)	19 (30.2)	0.740[f]	0.725
Christianity	40 (62.5)	43 (68.2)		
Traditional	2 (3.1)	1 (1.6)		
Occupation				
Unemployed	13 (20.3)	7 (11.1)	2.798[f]	0.424
Trader	10 (15.6)	13 (20.6)		
Artisan	6 (9.4)	9 (14.3)		
Professional	35 (54.7)	34 (54.0)		
Education				
None	2 (3.1)	0	2.520[p]	0.527
Primary	2 (3.1)	1 (1.6)		
Secondary	8 (12.5)	11 (17.4)		
Tertiary	52 (81.3)	51 (81.0)		
Tribe				
Yoruba	58 (90.6)	55 (87.3)	3.718[f]	0.255
Igbo	2 (3.1)	6 (9.5)		
Hausa	2 (3.1)	0		
Others	2 (3.1)	2 (3.2)		
Parity				
0	10 (15.6)	4 (6.3)	4.305[p]	0.116
1-3	43 (67.2)	52 (82.6)		
≥4	11 (17.2)	7 (11.1)		
Previous caesarean section				
0	34 (53.1)	34 (54.0)	2.571[f]	0.463
1	20 (31.3)	18 (28.6)		
2	8 (12.5)	11 (17.5)		
3	2 (3.1)	0		
Indications for caesarean section				
Maternal request	5 (7.8)	0	9.338[f]	0.053
Previous caesarean section	30 (46.9)	25 (39.7)		
Fetal macrosomia	13 (20.3)	13 (20.6)		
Elderly primigravia	12 (3.1)	8 (12.7)		
Others	14 (21.9)	17 (27.0)		
Gestational at delivery (weeks)	38.14±1.50	38.16±1.53	−0.067[t]	0.946
BMI (kg/m^2)	30.40±6.88	28.87±4.36	1.501[t]	0.136

[p]Pearson Chi-square, [f]Fisher's exact, [t]*t*-test. BMI: Body mass index, SD: Standard deviation

participants (3.1%) in Group A experienced somnolence and none in Group B. In all, there were no significant difference in side effect profiles of oral morphine and intramuscular pethidine ($P > 0.05$). More women required rescue analgesia in Group A (26.6%) than Group B (14.3%), but there was no statistically significant difference in the need for rescue analgesia between the two groups ($P = 0.086$) as shown in Table 3.

Discussion

This study aimed at comparing the efficacy of multiple doses of 10 mg oral morphine with that of 50 mg intramuscular pethidine in the treatment of postcaesarean pain among patients that underwent elective caesarean section. The sociodemographic data of the participants in both groups are similar. Majority of the participant are in the age range of 30–39 years reflecting the increasing age of child bearing in women likely due to educational pursuit of women and subsequent delay in getting married. Majority of the participants are Yorubas who were observed to have low pain threshold. This, if anything, would have been reflected as increase in the reported pain scores based on the report from a study in South-western Nigeria where majority of participants from this

Table 2: Mean pain intensity difference of both groups at rest and on movement

Variables	Mean±SD (range)		Mean difference	95% CI of mean difference	*t*-test	*P*
	Treament A: Morphine (*n*=64)	Treatment B: Pethidine (*n*=63)				
PID (t_{i+1}-t_i) at rest at 8 h	10.50±27.26 (−56-56)	12.57±25.93 (−32-64)	−2.071	−11.419-7.276	−0.439	0.662
PID (t_{i+1}-t_i) on movement at 8 h	19.00±27.66 (−40-64)	18.29±30.32 (−40-72)	0.714	−9.476-10.904	0.139	0.890
PID (t_{i+1}-t_i) at rest at 16 h	3.00±27.21 (−64-40)	4.19±27.29 (−56-48)	−1.190	−10.763-8.382	−0.246	0.806
PID (t_{i+1}-t_i) on movement at 16 h	10.63±27.79 (−40-56)	10.54±29.68 (−48-56)	0.085	−10.011-10.182	0.017	0.987
PID (t_{i+1}-t_i) at rest at 24 h	−7.5±26.93 (−72-48)	−8.25±27.79 (−64-48)	0.754	−8.855-10.363	0.155	0.877
PID (t_{i+1}-t_i) on movement at 24 h	−0.50±25.37 (−56-56)	−3.30±29.65 (−64-48)	2.802	−6.942-12.545	0.569	0.570
Spid at rest	6.00±76.72 (−192-120)	8.51±77.60 (−144-144)	−0.836	−6.497-4.825	−0.439	0.662
Spid on movement	29.13±75.25 (−112-120)	25.52±28.47 (−152-160)	1.200	−4.763-7.163	0.139	0.890

PID: Pain intensity difference, CI: Confidence interval

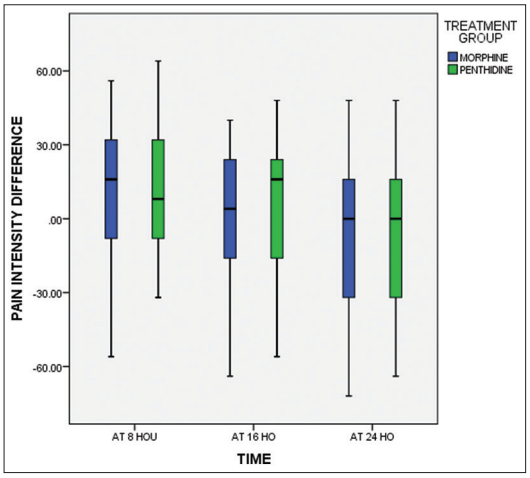

Figure 2: Variation of pain intensity different at rest with time

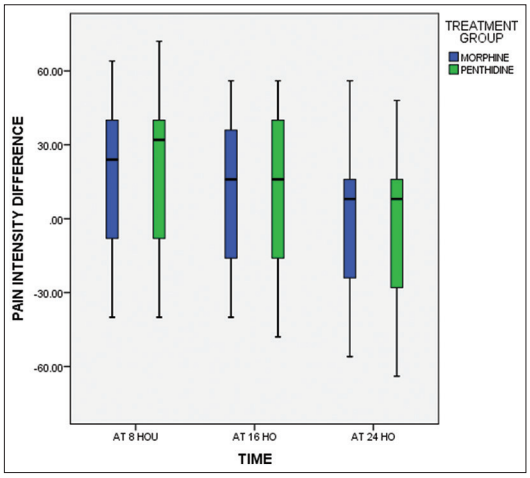

Figure 3: Variation of pain intensity difference on movement with time in the study groups

race had described exaggerated pain and required additional analgesia during labour.[14] Most of the participants have tertiary education, high educational status is said to reduce pain perception as people with low education tend to experience more pain, likely due to lack of understanding of preoperative counseling. The mean gestational age at delivery is similar in both groups (38.14 ± 1.50 and 38.16 ± 1.53 P = 0.946). Elective caesarean section is usually done at 38 weeks in our centre. Maternal weight for both groups was similar with mean BMI of 30.40 ± 6.88 and 28.87 ± 4.36 for the oral morphine and intramuscular pethidine group respectively (P = 0.136). Increasing BMI has been linked with increase pain threshold.[15] Most of the participants are multipara with previous experience which may influence their pain perception as they may have come to accept that some degrees of pain may be associated with child birth. The most common indication for caesarean section in this study was previous caesarean section. This finding is similar to that of previous studies where previous caesarean sections were reported as the commonest indication for caesarean section.[9,11,16] Repeat caesarean section is associated with more pain likely due to adhesions.

The use of different oral opioids in the management of postcaesarean pain has been documented but, there is still lack of sufficient of evidence to recommend its use.[9,11,17] Oral morphine was chosen for this study because it is becoming increasingly available in our environment and it has been shown to control postoperative pain. It was found in this study that oral morphine has similar efficacy to intramuscular pethidine in the control of postcaesarean section pain. The PID at rest was persistently lower in the oral morphine group over 24-h except at 8-h when it was slightly higher 19.00 ± 27.66 versus 18.29 ± 30.32 t = 0.139, P = 0.890) but, it was higher on movement than the intramuscular pethidine group (t = −0.439 P = 0.662). Oral morphine is more potent against incisional pain which is most intense during the first 24-h after surgery.[16] The SPID was lower in the oral morphine at rest but higher than the intramuscular pethidine group on movement though with no statistical difference (t = 0.139 P = 0.890). Bonnal *et al*. reported noninferiority of oral morphine when included in multimodal analgesic management of postcaesarean pain compared to multimodal parenteral analgesics.[11] The fear of side effect has been one of the hindrances to the use of opioids. One the most feared side effect is somnolence which may impair the ability of the new mother to care for her baby. Only two (3.1%) of the participants in the morphine group had somnolence and this was not statistically significant (X^2 = 2.773 P = 0.496). This is

Table 3: Side effects of the drugs and need for rescue analgesia in treatment groups

Variable	Treament A: Morphine ($n=64$), n (%)	Treatment B: Penthidine ($n=63$), n (%)	χ^2/Fisher's exact	P
Nausea				
Yes	0	0	0.000	1.000
No	64 (100.0)	63 (100.0)		
Vomiting				
Yes	0	0	0.000	1.000
No	64 (100.0)	63 (100.0)		
Pruritis				
Yes	0	0	0.000	1.000
No	64 (100.0)	63 (100.0)		
Somnolence				
Yes	2 (3.1)	0	2.773	0.496
No	62 (96.9)	63 (100.0)		
Respiratory distress				
Yes	0	0	0.000	1.000
No	64 (100.0)	63 (100.0)		
Rescue analgesia				
Yes	17 (26.6)	9 (14.3)	2.939	0.086
No	47 (73.4)	54 (85.7)		
VAS score	8	8		0.260

VAS: Visual Analog Scale

similar to the findings of Bonnal *et al*.[11] where somnolence was reported in 3% of their participants who had oral morphine as part of postcaesarean analgesia, they also reported 18%, 7% and 3% for nausea, vomiting, and pruritus, respectively. These side effects; nausea, vomiting, pruritus, and respiratory distress were however not experienced by any participants in either arm of this present study. The low side effect experienced by the participants in this study may be attributed to race, blacks have an increase morphine clearance compared to other races as reported by Sadhasivam *et al*.[18] The request for rescue analgesia was more in the oral morphine group than the intramuscular pethidine group. This may be due to the slower onset of action of oral morphine compared to intramuscular pethidine ($P = 0.086$).

The median VAS score for maternal satisfaction was similar for both groups (8 and 8 $P = 0.260$). Contrary to this study, some authors reported high maternal satisfaction with oral analgesia compared to parenteral analgesia in the management of postcaesarean pain and the preference for oral analgesia was attributed to the avoidance of the pain induced by parenteral administration.[11,16]

Conclusion

This prospective study was able to prove that oral morphine offers equal analgesia compared to intramuscular pethidine in the management of postcaesarean pain. Maternal satisfaction with oral morphine is similar to intramuscular pethidine. Oral morphine has little or no side effects when used in the immediate postcaesarean period in our environment. Hence, oral morphine is an acceptable alternative to intramuscular pethidine in the management of postcaesarean section pain.

Limitation

This is a novel study in our environment; hence, there was limited guidance to follow in the conduct of this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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