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Effectiveness of Subcutaneous Bupivacaine–Ketamine Wound Infiltration in Reducing Post-Cesarean Section Pain: A Randomized, Double-Blind, Controlled Trial

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Abstract

Background: Effective postoperative analgesia supports maternal recovery after cesarean delivery, yet subcutaneous local anesthetic infiltration, a simple technique well suited to resource-limited settings, typically provides only 3–6 hours of relief. Ketamine, an NMDA-receptor antagonist with analgesic activity at subanesthetic doses, may extend this window, but evidence in cesarean delivery remains limited.
Objective: To determine whether adding subcutaneous ketamine to bupivacaine infiltration reduces rescue opioid requirement after cesarean delivery.
Methods: In this randomized, double-blind, controlled trial at Tangerang Regional General Hospital, Indonesia, 60 women undergoing cesarean delivery under spinal anesthesia were allocated 1:1 to subcutaneous infiltration of 0.25% bupivacaine with ketamine 0.9 mg/kg (Group A, n = 30) or 0.25% bupivacaine alone (Group B, n = 30) before wound closure. The primary outcome was total rescue fentanyl requirement in the first 24 postoperative hours.
Results: The median 24-hour fentanyl requirement was lower with ketamine (30 [0–90] vs 90 [0–150] mcg; $p < 0.001$), and fewer participants required rescue fentanyl at all (56.7% vs 76.7%), with a lower cumulative group dose (840 vs 2240 mcg). Group A also had lower pain scores from hour 7 onward, a longer interval to the first rescue request (810 vs 420 min; $p = 0.019$), and earlier first mobilization (585 vs 810 min; $p < 0.001$). No serious adverse events occurred in either group.
Conclusion: Adding subcutaneous ketamine to bupivacaine infiltration lowered the rescue opioid requirement and supported faster recovery after cesarean delivery, offering a practical, low-cost addition to multimodal analgesia in resource-limited settings.

Keywords: *ketamine; bupivacaine; subcutaneous infiltration; postoperative pain; cesarean section*

Introduction

Cesarean section is one of the most frequently performed operations worldwide, and in Indonesia the proportion of deliveries by this route rose from 5% in 2012 to 17% in 2017.[1] Acute pain after cesarean delivery remains poorly controlled in many settings: 78.4–92.7% of women in developing countries report moderate-to-severe pain in the first postoperative days, a substantially higher rate than in high-income countries.[2] Beyond the immediate discomfort, unrelieved pain increases opioid requirement, delays mobilization and breastfeeding, disrupts early mother–infant contact, and is an established risk factor for both postpartum depression and persistent post-surgical pain.[2]

Part of this gap reflects the analgesic options that are realistically available. In many resource-limited hospitals, postoperative analgesia after cesarean delivery still relies mainly on paracetamol and NSAIDs, whereas higher-income settings more often add opioids or peripheral nerve blocks.[2] Intrathecal morphine remains the reference standard because of its long duration of action, but preservative-free formulations suitable for intrathecal use are not consistently available.[3] The PROSPECT guideline instead recommends a bundle of simpler measures for cesarean delivery (intravenous NSAIDs and paracetamol, ilioinguinal/iliohypogastric or transversus abdominis plane block, and local anesthetic wound infiltration) that perform comparably well in the early recovery period.[4]

Of these options, subcutaneous local anesthetic infiltration is the most accessible: it requires no specialized equipment, can be performed by either the surgeon or the anesthesiologist, and is technically simpler than a nerve block. Its main drawback is duration: the analgesic effect typically lasts only 3–6 hours, fading at about the same time as intrathecal opioid analgesia wears off and leaving a gap in coverage during a clinically important window.[5]

Ketamine, a non-competitive NMDA-receptor antagonist with analgesic activity even at subanesthetic doses, has been proposed as an adjuvant to close that gap, in line with the opioid-sparing aims of Enhanced Recovery After Surgery (ERAS).[6] A 2024 systematic review and meta-analysis found that ketamine wound infiltration outperformed placebo during the first 9–12 postoperative hours.[7] A meta-analysis focused specifically on cesarean delivery similarly found that ketamine, used as an analgesic adjunct, reduced postoperative pain scores and opioid consumption after cesarean section.[20] Most trials combining ketamine with a local anesthetic, however, have used 0.5% bupivacaine; to our knowledge, none has tested the combination with 0.25% bupivacaine, the concentration more commonly used for subcutaneous infiltration in cesarean delivery.

We conducted this trial to determine whether adding ketamine to 0.25% bupivacaine infiltration at the cesarean incision would reduce the requirement for rescue analgesia. We hypothesized that ketamine would lower the 24-hour opioid requirement compared with bupivacaine alone.

Methods

Study Design and Setting

This randomized, double-blind, controlled trial was conducted in the obstetric operating theater of Tangerang Regional General Hospital (RSUD Kabupaten Tangerang), Indonesia, between February and March 2025. The target population comprised pregnant women scheduled for cesarean delivery under spinal anesthesia.

Participants

Women aged 18–45 years undergoing elective or emergency cesarean delivery via a Pfannenstiel incision under spinal (subarachnoid) anesthesia were eligible if they provided written informed consent. We excluded women who had used analgesic medication within 7 days before surgery, had a diagnosis of chronic pain or a hypertensive disorder of pregnancy (chronic, gestational, or pre-eclamptic), had a known allergy to bupivacaine, ketamine, paracetamol, ketorolac, or fentanyl, or had an intellectual disability, thought disorder, or other condition that would impair subjective pain assessment. Participants were withdrawn if the operation was extended by uterine resection, hysterectomy, or further pelvic or abdominal exploration; if a further surgical procedure was required during the same admission; if spinal anesthesia was converted to general anesthesia for any reason; or at their own request. Participants were enrolled consecutively according to the surgical schedule.

Sample Size

The sample size was calculated for a two-group comparison of independent means, based on the anticipated between-group difference in 24-hour rescue fentanyl requirement. A difference of 60 mcg was considered clinically meaningful, with a pooled standard deviation of 79.3 mcg taken from earlier studies of rescue fentanyl requirement. At a two-sided α of 5% and 80% power, the minimum sample size was 28 participants per group; allowing for an anticipated 10% loss to follow-up, we enrolled 30 participants per group (total n = 60).

Randomization and Blinding

After eligibility was confirmed, participants were randomized 1:1 using a permuted-block sequence generated on the Sealed Envelope™ platform. Allocation was concealed using sequentially numbered, opaque, sealed envelopes held only by a research assistant with no role in direct patient care; envelopes were opened immediately before surgery began. The assistant prepared the infiltration solution according to the assigned group and handed it to the investigator performing the infiltration; both the investigator and the participant remained blinded to allocation throughout the study.

Study Protocol

Group A (ketamine group) received subcutaneous infiltration of 40 mL of 0.25% bupivacaine combined with ketamine 0.9 mg/kg body weight; Group B (control group) received 40 mL of 0.25% bupivacaine alone. The 0.25% solution was prepared by diluting plain 0.5% bupivacaine (Marcain®) 1:1 with 0.9% saline; ketamine was drawn from a 50 mg/mL stock solution and dosed according to body weight.

Spinal anesthesia was administered at the L3–L4 or L4–L5 interspace with the patient seated, using hyperbaric 0.5% bupivacaine 10 mg combined with intrathecal fentanyl 25 mcg, after standard monitoring (non-invasive blood pressure, electrocardiography, and pulse oximetry). Intraoperative fluid and drug management was determined by the attending anesthesiologist independently of the study protocol. Once the infant was delivered and the uterine layer closed (at the point at which the surgeon began closing the fascial layer), all participants received intravenous paracetamol 1000 mg and ketorolac 30 mg, repeated every 8 hours as scheduled maintenance analgesia; the timing of this first dose served as the reference point for subsequent dosing.

Before subcutaneous and skin closure, the investigator infiltrated the assigned solution at 10 points along the Pfannenstiel incision (five along the superior margin and five along the inferior margin, spaced 3–4 cm apart), with approximately 4 mL per point via a 23-gauge needle. Wound closure proceeded immediately thereafter. Participants who required conversion to general anesthesia or met any other withdrawal criterion intraoperatively were withdrawn from the study, and the reason was recorded.

Outcome Measures

The time of subcutaneous infiltration served as the reference point for postoperative pain assessment. Pain intensity was assessed using the Numeric Rating Scale (NRS, 0–10) at 1, 2, 6, 12, and 24 hours after infiltration, with participants re-briefed on the scale before each assessment. Rescue analgesia (intravenous fentanyl 30 mcg) was administered whenever a participant reported bothersome pain or an NRS score ≥4, with a minimum interval of 10 minutes between doses, a maximum cumulative dose of 100 mcg per hour, and 400 mcg per day. The time to first request for rescue analgesia and the total 24-hour dose were recorded for each participant.

The primary outcome was total rescue fentanyl requirement in the first 24 postoperative hours. Secondary outcomes were time to onset of pain, time to peak pain intensity, NRS scores across four 6-hour intervals, time to first rescue analgesia request, time to first postoperative mobilization, and treatment-related adverse events. Baseline demographic and clinical data, including age, body mass index, ASA physical status, comorbidities, obstetric history, and intraoperative details, were recorded from medical records and structured case report forms. Data from participants who withdrew were excluded from outcome analysis but reported descriptively.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY) on a per-protocol basis. Categorical variables were presented as frequencies and percentages, and numeric variables as mean ± standard deviation for normally distributed data or median (minimum–maximum) for non-normally distributed data, as determined by the Shapiro–Wilk test. Between-group comparisons used the independent-samples t-test or

Mann–Whitney U test for numeric variables, and the chi-square or Fisher's exact test for categorical variables, as appropriate. A two-sided p-value < 0.05 was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Health Research Ethics Committee of Tangerang Regional General Hospital (approval number 000.9.2/010 KEP RSUTNG), and institutional research permission was granted by the same hospital. Written informed consent was obtained from all participants before enrollment.

Results

Participant Flow

Of 81 women screened for eligibility during the study period (Figure 1), 21 were excluded because of a hypertensive disorder of pregnancy (n = 18), a psychiatric disorder (n = 2), or malignancy-related chronic pain (n = 1). The remaining 60 participants were randomized, 30 to each group, and all completed the study through primary outcome assessment; no participant was withdrawn for conversion to general anesthesia or for any other criterion.

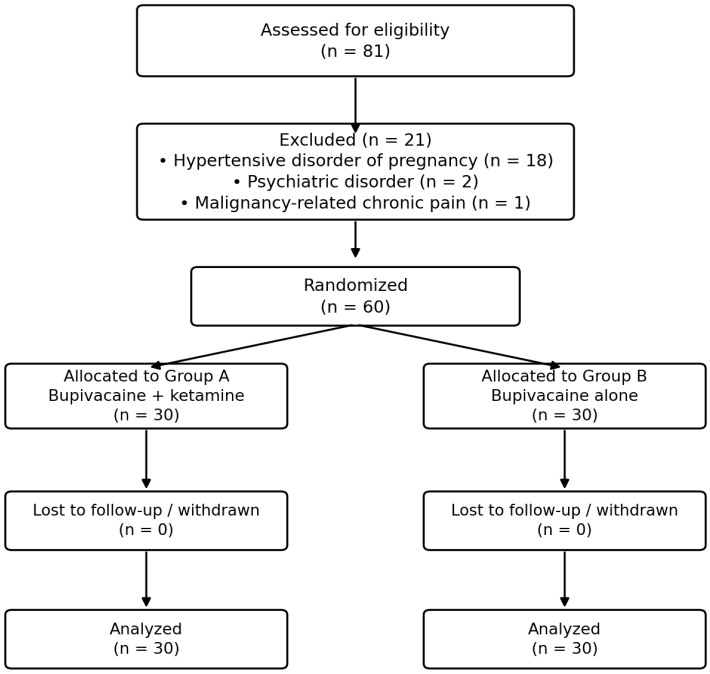

Figure 1. CONSORT flow diagram of participant enrollment, allocation, follow-up, and analysis.

Baseline Characteristics

The groups were comparable at baseline (Table 1): age, BMI, ASA physical status, comorbidity profile, obstetric history, and extent of uterine exteriorization did not differ significantly (all p > 0.05). The duration of surgery was slightly shorter in the ketamine group (90 [70–125] vs 100 [70–135] min; p = 0.028), and incision length was similar between the groups.

Table 1. Baseline characteristics of study participants

Variable	Group A (bupivacaine + ketamine) (n = 30)	Group B (bupivacaine alone) (n = 30)	p-value
Age (years)	30 (18–44)	33.5 (17–39)	0.402†

Variable	Group A (bupivacaine + ketamine) (n = 30)	Group B (bupivacaine alone) (n = 30)	p-value
BMI (kg/m²)	26.7 (17.9–37.9)	27.2 (13.9–32.8)	0.836†
ASA II, n (%)	29 (96.7)	29 (96.7)	1.000††
ASA III, n (%)	1 (3.3)	1 (3.3)	
Anemia, n (%)	8 (26.7)	10 (33.3)	1.000‡
Undernutrition, n (%)	1 (3.3)	1 (3.3)	1.000††
Obesity, n (%)	21 (70.0)	23 (76.7)	0.559‡
Hyperthyroidism, n (%)	1 (3.3)	0 (0)	1.000††
HIV, n (%)	1 (3.3)	2 (6.7)	1.000††
Pulmonary tuberculosis, n (%)	0 (0)	2 (6.7)	0.492††
Primigravida, n (%)	7 (23.3)	6 (20.0)	0.754‡
Multiparity, n (%)	22 (73.3)	24 (80.0)	0.542‡
Previous cesarean – none, n (%)	18 (60.0)	15 (50.0)	0.505‡
Previous cesarean – 1, n (%)	7 (23.3)	8 (26.7)	
Previous cesarean – 2, n (%)	5 (16.7)	5 (16.7)	
Previous cesarean – 3, n (%)	0 (0)	2 (6.6)	
Uterine exteriorization, n (%)	18 (60.0)	18 (60.0)	1.000‡
Duration of surgery (min)	90 (70–125)	100 (70–135)	0.028†
Incision length (cm)	11 (10.5–12.5)	11 (10–12)	0.811†

†Median (minimum–maximum), Mann–Whitney U test. ††n (%), Fisher's exact test. ‡n (%), chi-square test.

Postoperative Pain Assessment and Rescue Analgesia Requirement

Postoperative pain outcomes are summarized in Table 2. Time to onset of pain and time to peak pain intensity were similar between the groups (p = 0.316 and p = 0.953, respectively), as was the peak NRS score during the first 6 postoperative hours (p = 0.105). From hour 7 onward, however, the ketamine group reported lower peak NRS scores at every subsequent interval (p = 0.004, p = 0.001, and p < 0.001 for hours 7–12, 13–17, and 18–24, respectively). No participant in either group reported severe pain (NRS 8–10) at any time point. Moderate pain (NRS 5–7) as the worst pain reported within 24 hours was numerically less common with ketamine, although the difference was not statistically significant (53.3% vs 73.3%; p = 0.108). Time to first mobilization was shorter with ketamine (median 585 [420–980] vs 810 [450–1400] min; p < 0.001), and fewer participants in the ketamine group required rescue fentanyl at all (56.7% [17/30] vs 76.7% [23/30]), although this difference was not statistically significant (p = 0.100).

Table 2. Acute postoperative pain assessment after cesarean section

Variable	Group A (bupivacaine + ketamine) (n = 30)	Group B (bupivacaine alone) (n = 30)	p-value
Time to onset of pain (h)	5 (4–10)	4.5 (5–8)	0.316†
Time to peak pain intensity (h)	11 (4–17)	10 (4–19)	0.953†
Peak NRS, hour 0–6	2 (0–6)	2 (0–6)	0.105†
Peak NRS, hour 7–12	2 (1–6)	4 (1–7)	0.004†

Variable	Group A (bupivacaine + ketamine) (n = 30)	Group B (bupivacaine alone) (n = 30)	p-value
Peak NRS, hour 13–17	3 (2–5)	4 (2–7)	0.001†
Peak NRS, hour 18–24	3 (2–5)	4 (2–7)	<0.001†
Mild pain (NRS 1–4), n (%)	14 (46.7)	8 (26.7)	0.108‡
Moderate pain (NRS 5–7), n (%)	16 (53.3)	22 (73.3)	
Time to first mobilization (min)	585 (420–980)	810 (450–1400)	<0.001†
Required rescue fentanyl, n (%)	17 (56.7)	23 (76.7)	0.100‡

†Median (minimum–maximum), Mann–Whitney U test. ‡n (%), chi-square test.

Time to First Rescue Analgesia Request

Among the 40 participants who requested rescue analgesia, those in the ketamine group waited approximately twice as long before their first request (median 810 [250–1070] vs 420 [230–1050] min; p = 0.019) (Table 3).

Table 3. Time to first request for rescue analgesia

Variable	Group A (n = 17)	Group B (n = 23)	p-value
Time to first fentanyl request (min)	810 (250–1070)	420 (230–1050)	0.019†

†Median (minimum–maximum), Mann–Whitney U test. n reflects only participants who requested rescue analgesia.

Adverse Events

No serious adverse events, surgical wound infections, or difficulties in wound closure occurred in either group. Nausea (4/30 in each group) and vomiting (2/30 in each group) occurred with equal frequency in both groups, and neither group reported dysphoria, hallucination, or vivid dreaming. Nystagmus was the most frequently observed event, occurring in 24 of 30 participants (80%) who received ketamine but in none of the control group; all episodes were transient and self-limited, and resolved without specific intervention.

Discussion

Effect on Pain Perception and Analgesic Duration

Pain scores were lower with ketamine from hour 7 through hour 24 ($p < 0.005$), indicating a longer window of effective analgesia than bupivacaine alone provided. These findings were consistent with earlier double-blind trials. Aksoy et al. found that subcutaneous ketamine 1 mg/kg combined with bupivacaine reduced both resting and cough-evoked pain for up to 12 hours after cesarean delivery,[9] and Behaeen et al. reported lower pain scores at 2, 4, 6, and 12 hours with ketamine 0.5 mg/kg given either before or after skin incision, with no difference between the two timings.[8] Rizk et al. described a longer pain-free interval and higher patient satisfaction with bupivacaine–ketamine than with bupivacaine alone,[10] and Mishra et al. similarly found lower pain scores in the first 4 postoperative hours with ketamine infiltration compared with ropivacaine.[11] Manouchehrian and Behboodi also reported lower postoperative pain scores with subcutaneous ketamine infiltration compared with control in women undergoing elective cesarean delivery under spinal anesthesia.[21]

Not all trials have agreed. Zohar et al., testing patient-controlled bupivacaine wound instillation after cesarean delivery, found that adding ketamine 1 mg/mL made no difference to pain at rest, with coughing, or with leg elevation, and both arms still required similar cumulative rescue morphine (11.2 ± 4.6 vs 11.3 ± 5.6 mg); they attributed this null result to possibly subtherapeutic dosing, limited peripheral penetration of ketamine, or a

ceiling effect not reached by their regimen.[12] This discrepancy points to dose, administration technique (infiltration versus instillation), and background analgesic regimen as likely explanations, and argues for caution when comparing studies with different protocols.

The analgesic effect observed in this study probably involved more than NMDA-receptor blockade alone. Ketamine also inhibits the NF-κB signaling pathway, which drives the expression of pro-inflammatory mediators such as interleukin-6 (IL-6) and C-reactive protein (CRP): Sun et al. demonstrated this suppression in macrophages,[13] and Bartoc et al. found that even a small induction dose of ketamine lowered perioperative IL-6 and CRP levels.[14] Central antinociception combined with local anti-inflammatory activity may together explain the extended analgesia observed in this trial. Pain perception is nonetheless shaped by factors we did not measure directly (education, prior pain experience, and comorbidity), although the relatively homogeneous, single-center population and the double-blind design make it unlikely that these factors differed systematically between the groups.

Opioid-Sparing Effect

Ketamine roughly doubled the time to the first rescue request (810 vs 420 min; $p = 0.019$), although the proportion of participants requiring any rescue opioid did not differ significantly between the groups (56.7% vs 76.7%; $p = 0.100$). Together with the lower 24-hour fentanyl dose reported above, this pattern was consistent with a genuine opioid-sparing effect rather than a chance finding. Abate et al.'s meta-analysis found that ketamine wound infiltration delayed the first analgesic request by a mean of 1.56 hours compared with bupivacaine alone (95% CI 0.04–3.08; $p = 0.04$),[7] Aksoy et al. reported a lower postoperative morphine requirement with local ketamine after cesarean delivery,[9] and Afify and Mahdy found the same pattern after open abdominal hysterectomy, where ketamine reduced the 24-hour opioid requirement and prolonged analgesia compared with fentanyl-based infiltration.[15]

The pattern extended beyond obstetric surgery. Mohamed et al. found that ketamine 2 mg/kg combined with bupivacaine reduced morphine use and prolonged pain-free time after abdominal hysterectomy ($p < 0.05$),[16] Raj et al. reported fewer fentanyl demands after mastectomy with bupivacaine–ketamine than with bupivacaine alone or bupivacaine–dexmedetomidine,[17] and Rizk et al. again found lower morphine use with bupivacaine–ketamine than with bupivacaine alone after cesarean delivery.[10] That the effect appeared across such different procedures argues for a genuine pharmacological mechanism rather than an effect specific to our setting.

Effect on Postoperative Recovery

Participants who received ketamine mobilized sooner than those in the control group (median 585 vs 810 min; $p < 0.001$). Direct evidence on ketamine infiltration and mobilization time after cesarean delivery is scarce; Eftekhar et al. found that subcutaneous ketamine 0.5 mg/kg after abdominal hysterectomy lowered pain scores and opioid requirement but did not assess mobilization directly.[18] Better pain control plausibly accelerates mobilization by reducing guarding behavior and movement-related pain avoidance and by improving sleep quality,[19] but we did not adjust for other likely contributors, such as residual neuraxial motor block and nursing practice, so this association should be interpreted as suggestive rather than conclusive.

Limitations

Several limitations should be weighed against these findings. The trial was conducted at a single center, which may limit generalizability; multicenter data from more varied populations and care settings would strengthen the evidence. The Numeric Rating Scale, although practical, has known limits in specificity and sensitivity, and pain was assessed only at rest, without distinguishing static from movement-evoked pain. Rescue fentanyl was given as a fixed 30-mcg dose regardless of body weight, which may have produced an inconsistent analgesic effect across participants of different sizes; weight-based dosing will improve precision in future studies. Finally, functional recovery was represented only by time to first mobilization; we did not assess specific milestones

such as independent sitting or standing, nor broader recovery measures such as length of hospital stay or neonatal wellbeing.

Conclusions

Adding ketamine 0.9 mg/kg to subcutaneous 0.25% bupivacaine infiltration lowered the rescue fentanyl requirement, extended the pain-free interval, and shortened the time to mobilization after cesarean delivery, without serious adverse effects. These findings supported subcutaneous ketamine as a practical, low-cost addition to multimodal analgesia, particularly where resources for opioid-based or regional techniques are limited.

Recommendations for Future Research

Multicenter trials in more heterogeneous populations will help to confirm generalizability. Future studies will need to use finer-grained pain instruments, weight-based rescue dosing, and broader recovery outcomes (length of stay, mother–infant interaction, and systemic ketamine effects), and will need to compare pre- versus post-incisional timing and different infiltration depths directly in order to define an optimal regimen. Head-to-head trials against other adjuvants such as ketorolac or dexamethasone will also help to clarify ketamine's relative place in preventing persistent post-cesarean pain.

Declarations

Ethics approval and consent to participate

This study was approved by the Health Research Ethics Committee of Tangerang Regional General Hospital and conducted with institutional research permission from the same hospital. Written informed consent was obtained from all participants before enrollment.

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This study was conducted as part of the corresponding author’s postgraduate thesis requirement at the Faculty of Medicine, Universitas Indonesia, and received no external funding.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

NS conceived and designed the study, performed data collection and the intervention, analyzed the data, and drafted the manuscript. RF, BS, and RIS supervised the study design and conduct, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declaration concerning generative AI and AI-augmented technologies in the compositional process

In the course of preparing this paper, the authors utilized ChatGPT to enhance readability and linguistic quality. Subsequent to utilizing this tool/service, the writers assessed and amended the information as necessary and assume complete accountability for the publication's content.

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