

The Median Effective Dose of Oxytocin Needed to Prevent Uterine Atony During Cesarean Delivery in Elderly Parturients

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Purpose: Oxytocin is the first-line agent to prevent and treat uterine atony during cesarean delivery (CD). We compared the effective dose in 50% of the parturients (ED₅₀) of a prophylactic oxytocin bolus during CD in young (<35 years) and old parturients (≥35 years) using Dixon's up-and-down method.

Patients and Methods: Twenty-eight young parturients (young group) and 25 old parturients (old group) undergoing CD under combined spinal-epidural anesthesia were enrolled. The initial oxytocin bolus was 0.5 IU, with increments or decrements of 0.25 IU. Maternal adverse effects, requirement for additional uterotonic agents, and estimated blood loss were recorded.

Results: The ED₅₀ for oxytocin in the old group was higher than that in the young group (1.41 IU; 95% confidence interval, 0.63–2.19) vs 0.66 IU (0.04–1.29), $P < 0.001$). The total oxytocin dose in the old group was higher than in the young group (5.9 ± 2.9 vs 4.1 ± 2.1 IU, $P = 0.01$). The estimated blood loss in the older group and young group was 401.2 ± 204.5 mL and 289.3 ± 104.6 mL, respectively ($P = 0.01$). The overall prevalence of adverse effects was higher in the old group than in the young group (68.0% vs 21.4%, $P < 0.001$).

Conclusion: The initial bolus and total requirement of oxytocin for preventing uterine atony were higher in old parturients than in young parturients during CD. Advanced maternal age may necessitate higher doses of oxytocin.

Keywords: maternal age, drug delivery, bolus, postpartum haemorrhage prevention

Introduction

Over recent decades, the mean maternal age in “developed” countries has been increasing gradually. Parturients over the age of 35 years have started to comprise an important proportion of the pregnant population.^{1,2} In China, the government estimated that 60% of the women who have benefited from the universal two-child policy are older than 35 years.³ Older age is associated with a significantly increased risk of intrapartum complications (eg, requirement for cesarean section and postpartum hemorrhage).^{4–6}

Smith and colleagues showed that spontaneous contraction of isolated myometrium during human pregnancy *ex vivo* decreased and exhibited increased multiphasic contractions with advancing maternal age.⁷ Also, myometrial tissue responds less effectively to oxytocin with increasing maternal age in the non-pregnant state.^{8,9} Also, parturients of advanced age are more likely to require oxytocin augmentation for induction of labor.⁹

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Oxytocin administration immediately after delivery of the fetus during cesarean delivery (CD) is recommended to prevent uterine atony and to treat established postpartum hemorrhage. The intravenous infusion dose of oxytocin after delivery during CD is controversial, so a universal dose for all cases is not appropriate.¹⁰

We hypothesized that older parturients would require more oxytocin to achieve an adequate uterine tone (UT) compared with that of their younger counterparts. We wished to investigate the effects of age on sensitivity to oxytocin during CD. We selected 53 patients scheduled for CD under spinal anesthesia to identify the effective dose in 50% of the parturients (ED₅₀) for oxytocin (using the Dixon up-and-down method (DUaDM¹¹) for an adequate UT between old (≥ 35 years) and young (<35 years) groups.

Patients and Methods

Ethical Approval of the Study Protocol

The present study was conducted in accordance with the principles stated in the Declaration of Helsinki 1964 and its later amendments. The study protocol was approved (2018-81) by the Ethics Committee of Jia Xing University Affiliated Women and Children Hospital (Jia Xing, China) in September 2018. Written informed consent was obtained from all participants. Our study was registered (30 May 2019) before patient enrolment in the Chinese Clinical Trial Registry (ChiCTR1900023469: Principal Investigator: CN Wei) and was conducted between 30 May and 20 December 2019.

Inclusion Criteria

The inclusion criteria were healthy parturients 1) with American Society of Anesthesiologists grade II; 2) between 18 and 45 years of age; 3) with a singleton pregnancy; 4) gestational age ≥ 37 weeks; 5) with a planned elective CD using the Pfannenstiel incision.

Exclusion Criteria

The exclusion criteria were as follows: 1) significant obstetric disease (including pregnancy-induced hypertension or pre-eclampsia); 2) body mass index ≥ 40 kg/m²; 3) active labor; 4) ruptured membranes; 5) previous resection of uterine fibroids; 6) known allergy to oxytocin; and 7) risk factors for postpartum hemorrhage (placenta previa, multiple gestations, macrosomia, polyhydramnios, uterine

fibroids, history of uterine atony and postpartum bleeding, or bleeding diathesis).

Study Groups

All parturients were divided into two groups based on age: young group (18–34 years of age) and old group (35–45 years of age). All parturients were treated with secondary CD and parity was 2. A history of CD was the primary indication for elective CD.

CD

Upon arrival in the operating theatre, an intravenous cannula was inserted in the dorsum of a hand. An infusion of Ringer's lactate solution (500 mL) was started 30 min before initiation of combined spinal-epidural anesthesia (CSE). Standard monitoring comprised five-lead electrocardiography, non-invasive blood pressure (NIBP) monitoring, heart rate (HR) and pulse oximetry. NIBP and heart rate were recorded every 3 min throughout CD. CSE was undertaken in the L3/4 interspace using the loss-of-resistance method. Spinal anesthesia was induced with 0.5% hyperbaric bupivacaine (9–12 mg) based on abdominal girth and vertebral-column length¹² to achieve a block height at the T5 dermatome. All parturients received supplemental oxygen via a nasal cannula at 3 L/min until delivery of the fetus. Intraoperative fluid management was at the discretion of a very experienced anesthetist who was not involved in the scientific aspects of this study.

“Hypotension” was defined as a systolic blood pressure <90 mmHg or a decrease >20% from baseline, and was treated with phenylephrine (100 μ g, i.v.). Parturients not responding to phenylephrine were treated with ephedrine (6 mg). “Tachycardia” was defined as HR ≥ 120 beats/min.

Immediately upon delivery of the fetus, one bolus of oxytocin (Nanjing Xinbai Pharmaceuticals, Nanjing, China) in a scaled syringe was administered (i.v.) over 5 s. The DUaDM was used to determine the oxytocin dose. The initial bolus of oxytocin was 0.5 IU for the first parturient in both groups. The oxytocin dose for the next parturient in the corresponding group was determined by the response of the previous parturient to a higher dose or lower dose of oxytocin. The increment or decrement was set as 0.25 IU for both groups. If the response of the previous parturient to the initial bolus of oxytocin was “adequate”, the dose for the next parturient was decreased by 0.25 IU. If the response of the previous parturient was “inadequate”, the dose for the next parturient was

increased by 0.25 IU. After delivery of the fetus, the obstetrician facilitated spontaneous delivery of the placenta with cord traction, but without uterine massage, after which the uterus was exteriorized. Two-layer sutures were adopted for the uterus. The UT was evaluated by a senior attending obstetrician (blinded to the study protocol) while undertaking CD (such as suture of the uterus, and stopping bleeding). The UT was evaluated 3, 6, and 9 min after oxytocin administration. The obstetrician evaluated the UT subjectively at each time point as “adequate” or “inadequate”. If the UT was considered to be adequate at 3 min, then an oxytocin infusion (3 IU oxytocin diluted in 20 mL of physiologic (0.9%) saline) at 3 IU/h was started. If the UT was considered inadequate 3 min after administration, then a “rescue” dose of oxytocin (3 IU) was administered within 30 s. If the UT remained inadequate after two rescue doses of oxytocin, an alternative uterotonic agent (methylergonovine maleate (0.2 mg, i. m.); carboprost tromethamine (0.25 mg, i.m.) or misoprostol (800–1000 mg, p.r.)) was administered.

The primary outcomes were an adequate or inadequate UT 3 min after the administration of the first dose of oxytocin, and the total requirement for oxytocin. Secondary outcomes were: total volume of crystalloid infused intravenously; delivery time for the placenta; estimated blood loss (quantified as the sum of blood in the suction canister and weight of blood on surgical sponges and the maternity pad); postoperative hemoglobin level (measured 30 min after CD completion); requirement for additional uterotonic agents; oxytocin-related adverse effects (hypotension, nausea, vomiting, headache, tachycardia, flushing, and chest pain). The lowest blood pressure during the 15-min interval after administration of the oxytocin bolus was recorded. Demographic characteristics, antepartum hemoglobin level, amniotic fluid volume (estimated by suction), fetal weight, and duration of the surgical procedure were also recorded.

Statistical Analyses

Data are the mean \pm SD, median (range), or the number of patients. Data were assessed for a normal distribution of variance using normality plots and the Kolmogorov–Smirnov test. Differences between groups were analyzed using an independent *t*-test or the Mann–Whitney *U*-test as appropriate. Binomial data were obtained using the chi-squared test, Yates correction, or Fisher’s exact test where appropriate. Statistical analyses were carried out using

SPSS 19.0 (IBM, Armonk, NY, USA). $P < 0.05$ was considered significant.

The ED₅₀ of the initial bolus of oxytocin after delivery was determined by calculating the mean of the midpoint of the pair of oxytocin doses in successive parturients in which an inadequate response was followed by an adequate response (crossover) according to the DUaDM.^{13–15}

The sample size was considered to be sufficient if six pairs of “crossover” points were obtained as the DUaDM was applied for ED₅₀ evaluation. Simulation studies using the DUaDM suggested that ≥ 20 patients should be included to obtain stable estimates.^{11,16} Increasing the number of crossovers could improve the ED₅₀ estimate, but the magnitude of the improvement would be small.¹⁷ We decided to obtain seven crossovers for the present study.

Results

Fifty-eight parturients were approached, of whom five declined to participate in our study. Fifty-three parturients were included in the final analysis: 28 in the young group and 25 in the old group. Demographic characteristics and CD details are shown in Table 1, which were similar between both groups except for maternal age, which was higher in the old group.

The subsequent response of each dose of oxytocin (adequate or inadequate) determined by the DUaDM is shown in Figure 1. The ED₅₀ of oxytocin using midpoint analyses was higher in the old group compared with that in the young group (1.41 IU; 95% confidence interval 0.63–2.19) vs 0.66 IU (0.04–1.29), $P < 0.001$). The dose–response curves of oxytocin in the two groups are shown in Figure 2. The total oxytocin requirement was higher in the old group compared with that in the young group (5.9 \pm 2.9 vs 4.1 \pm 2.1 IU, $P = 0.01$).

Secondary outcomes and adverse events are shown in Table 2. The estimated blood loss of the old group and young group was 401.2 \pm 204.5 mL and 289.3 \pm 104.6 mL, respectively, which was significantly different between the two groups ($P = 0.01$). The overall prevalence of adverse effects was higher in the old group compared with that in the young group (68.0% vs 21.4%, $P < 0.001$). Thirty-two percent of parturients in the old group required supplemental uterotonics compared with 10.7% in the young group ($P = 0.06$). None of the parturients in the two groups experienced tachycardia. The postoperative hemoglobin level, total volume of crystalloid administered, lowest

Table 1 Demographic Characteristics and Details of Cesarean Delivery

Variables	Young (n = 28)	Old (n = 25)	P
Age (years)	29.5 ± 3.7	37.7 ± 2.3	<0.001
Weight (kg)	68.8 ± 6.5	71.6 ± 6.6	0.13
Height (cm)	160.3 ± 3.5	159.6 ± 3.7	0.50
Body mass index (kg/m ²)	26.8 ± 2.5	27.6 ± 2.0	0.19
Gestational age (weeks)	39 (38, 40)	39 (38, 40)	0.64
Volume of amniotic fluid (mL)	595.7 ± 211.8	606.8 ± 241.6	0.86
Preoperative hemoglobin (g/L)	117.7 ± 10.3	113.2 ± 8.4	0.22
Blood pressure at baseline (mmHg)			
Systolic	102.3 ± 7.5	105.0 ± 8.7	0.21
Diastolic	51.6 ± 7.7	54.8 ± 8.7	0.16
Mean	71.9 ± 6.4	74.8 ± 7.2	0.12
Heart rate at baseline (beat/min)	89.8 ± 9.2	86.0 ± 10.1	0.16
Fetal weight (g)	3386.4 ± 333.4	3423.6 ± 281.1	0.11
Duration of CD (min)	41.8 ± 8.3	46.0 ± 9.8	0.10

Note: Data are the mean ± standard deviation or median (range).

blood pressure, and the delivery time for the placenta were similar between the two groups.

Discussion

We discovered that the ED₅₀ of the oxytocin bolus administered to prevent uterine atony during CD was almost two times greater in old parturients than in young parturients. Besides, the total oxytocin requirement was higher in the old group than in the young group. Our data will help clinicians understand and potentially “tailor” the amount of oxytocin administered to older parturients undergoing CD.

There has been considerable debate over the past decade surrounding the optimal dose and mode of oxytocin administration after delivery of the fetus during CD.^{10,18–20} The most recent consensus statements have suggested a bolus-and-infusion regimen for uterotonic administration for low-risk, elective CD, and CD in women during labor. A universal dose for all cases is not appropriate, and the optimal dose and mode of oxytocin administration for particular individuals is highly desirable.¹⁰ We chose to study the ED₅₀ of oxytocin by bolus because 1) this mode of administration, rather than an infusion, is common in China and 2) very low doses are required by infusion after an initial bolus.²¹

Bobrowski et al have performed a retrospective review of antepartum and delivery data of 9556 singleton pregnancies of women aged 20 to 29 or ≥35 years who delivered over 8 years, and found the elderly gravidas had the greatest age-related increases in oxytocin use (1.7times).²² Similarly, in the current study, parturients in the old group had a higher initial bolus dose of oxytocin, total oxytocin requirements, and estimated blood loss than those in the young group.

The mechanism of the age-induced increase in oxytocin demand for CD is incompletely understood. One possible explanation is that increasing maternal age is associated with reduced spontaneous activity of the myometrium and an increased likelihood of multiphasic contractions.⁷ These actions may lead to myometrial tissue responding less effectively to uterotonic agents (eg, oxytocin) with increasing maternal age, and scholars have observed this phenomenon.^{8,9,23} Arrowsmith and colleagues suggested that receptor expression/coupling to Ca²⁺ entry and contraction may decrease as maternal age advances.⁸ At the molecular level, Patel and colleagues found that expression of oxytocin receptors and connexin-43 mRNA was reduced in the myometrium from 8-month-old pregnant mice compared with that in 3-month-old pregnant mice. They documented a significant reduction in the copy number of mitochondrial-DNA in the

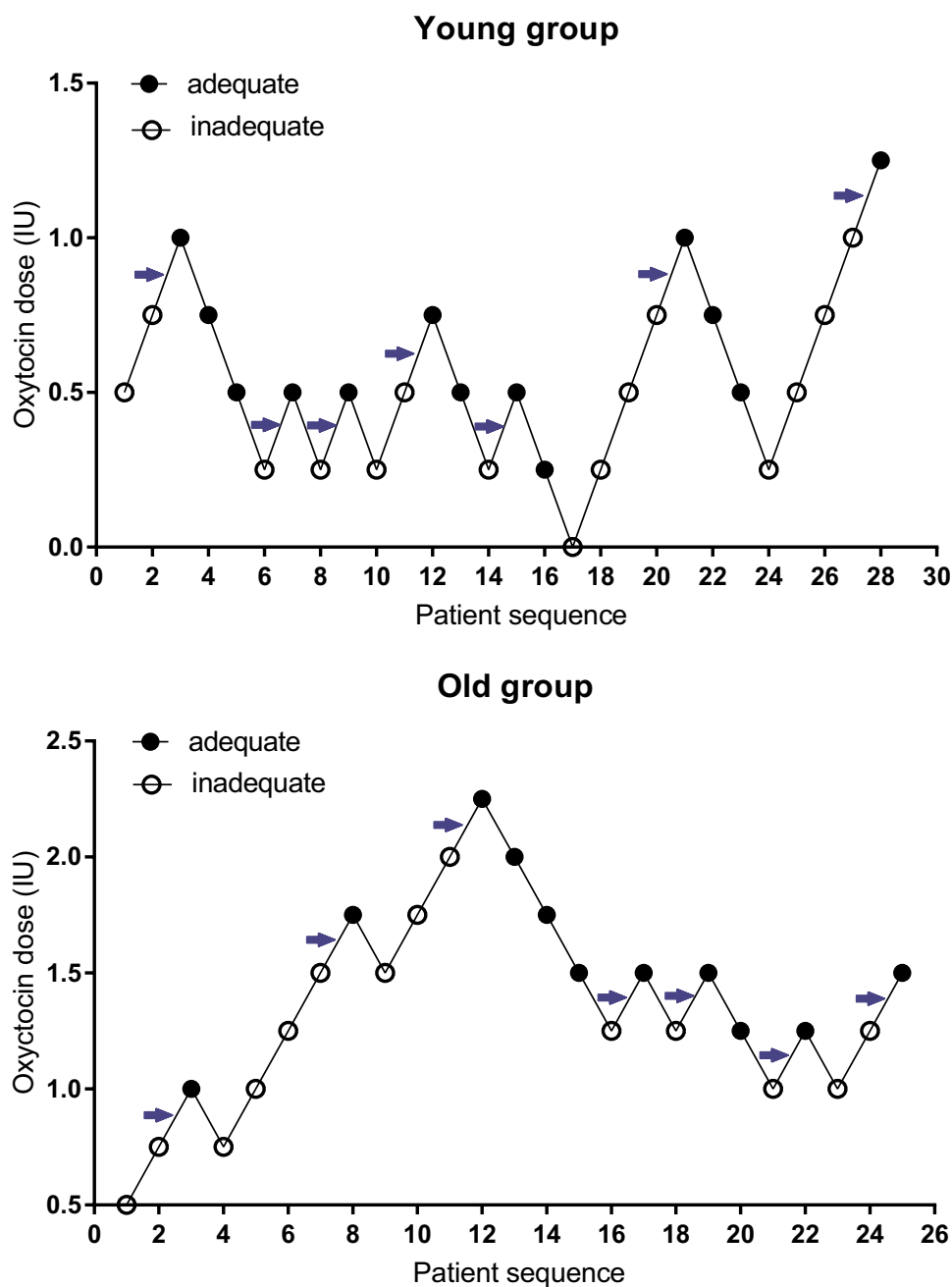


Figure 1 Dixon's up-and-down sequential allocation response (adequate or inadequate uterine tone 3 min after delivery) in young or old parturients after an initial oxytocin bolus. The initial dose in both groups was 0.5 IU, and the incremental change was 0.25 IU. The arrow shows seven midpoints of each group crossing from an "inadequate" uterine tone (empty circle) to "adequate" uterine tone (filled circle). The estimated effective dose in 50% of parturients was 0.66 IU (95% confidence interval, 0.04–1.29) in the young group and 1.41 IU (0.63–2.19) in the old group ($P < 0.001$).

myometrium from older mice. This action could contribute to impaired contractile activity via reduction in overall synthesis of adenosine triphosphate or altered regulation of intracellular Ca^{2+} .²⁴ The higher requirement of oxytocin to obtain an adequate UT in older parturients during CD may contribute to a decline in myometrial function.

Oxytocin is associated with adverse events such as hypotension, myocardial ischemia, arrhythmias, nausea,

vomiting, chest pain, headache, and flushing. A small dose and slow administration of oxytocin results in fewer adverse effects.^{25–27} Butwick and colleagues²⁸ undertook a dose–response study for oxytocin, and found that the prevalence of adverse effects increased with doses >1 IU. We also found a significant increase in overall side effects in the old group that received higher doses of oxytocin even though we adopted a slow rate of administration.

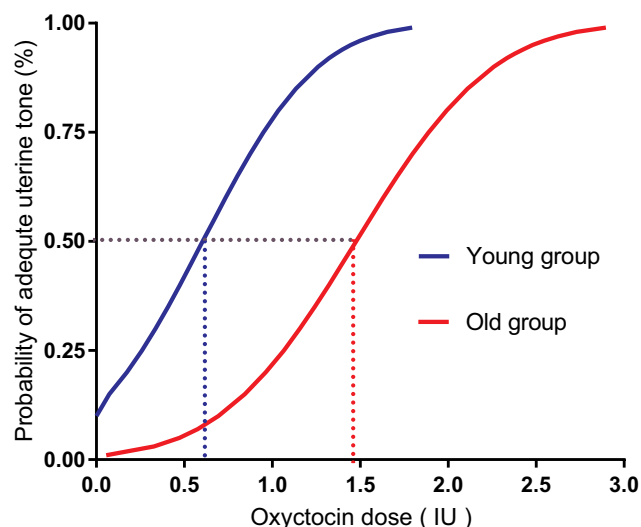


Figure 2 Dose–response curve of the oxytocin bolus needed to obtain an adequate uterine tone plotted from the estimated probabilities of an effective response (1%–100%) versus the corresponding oxytocin doses calculated using probit analyses.

Most of the studies investigating the relationship between advanced maternal age and postpartum hemorrhage have been retrospective, and many have not controlled for confounding variables (eg, maternal disorders).

Discrepancies exist in the literature.^{29,30} Several studies on the oxytocin dose for maintaining the UT during elective CD have been published,^{28,31,32} but none have focused on the effect of age on the oxytocin dose during CD. The present study was a double-blinded, dual-arm, dose–response study focusing on the effect of age on the oxytocin dose required to prevent uterine atony during CD. Our results suggest that obstetricians and anesthesiologists should consider the age of the parturient as a main factor when deciding the oxytocin dose for preventing uterine atony during CD.

Our study had four main limitations. First, analyses of the response to oxytocin and adverse effects 3 min after the initial bolus administration may have also been confounded by parturients accepting the rescue dose of oxytocin. However, we could not allow an inadequate UT and bleeding to continue untreated, so we adopted the “Rule of Three” algorithm.³³ Second, although senior attending obstetricians assessed the uterus, these assessments were subjective. However, objective evaluation methods are lacking, and our approach is similar to that of other scholars.^{21,26,31,32} Third, our study was designed to compare the ED₅₀ of a prophylactic oxytocin bolus during CD

Table 2 Secondary Outcomes and Adverse Events

	Young (n = 28)	Old (n = 25)	P
Estimated blood loss (mL)	289.3 ± 104.6	401.2 ± 204.5	0.01
Postoperative hemoglobin (g/L)	105.8 ± 12.5	98.3 ± 9.0	0.59
Total volume of crystalloid (i.v.) (mL)	960.0 ± 154.6	1060.0 ± 390.2	0.22
Total oxytocin dose (IU)	4.1 ± 2.1	5.9 ± 2.9	0.01
Delivery time of placenta (s)	129.3 ± 50.0	131.0 ± 47.9	0.90
Lowest blood pressure (mmHg)			
Systolic	98.3 ± 9.0	99.4 ± 13.2	0.73
Diastolic	46.5 ± 8.3	48.5 ± 11.1	0.45
Mean	69.3 ± 8.7	70.0 ± 10.5	0.78
Supplemental uterotonic agents	3 (10.7)	8 (32.0)	0.06
Adverse effects			
Overall	6 (21.4)	17 (68.0)	0.001
Headache	0 (0)	3 (12.0)	0.20
Nausea and/or vomiting	1 (3.6)	4 (16.0)	0.28
Chest pain	4 (14.3)	8 (32.0)	0.12
Flushing	1 (3.6)	2 (8.0)	0.92
Hypotension	3 (10.7)	5 (20.0)	0.45
Tachycardia	0 (0)	0 (0)	1

Note: Data are the mean ± standard deviation or number (%).

but, in clinical practice, many anesthetists and obstetricians may prefer to administer oxytocin at a dose closer to the ED₉₀ or ED₉₅ to obtain an adequate UT to prevent postpartum hemorrhage. Further studies investigating the effect of oxytocin on higher points on the dose–response curve may be of interest. Fourth, although the attending obstetricians were blinded to the oxytocin dose administered, they were aware of the age difference between the two groups. Hence, they may have had a different threshold for an adequate UT in either group.

Conclusions

The ED₅₀ of the oxytocin bolus administered during the third stage of labor was significantly higher in older parturients compared with that in younger parturients undergoing elective CD. These results are consistent with reports of a greater oxytocin requirement in older parturients.^{9,22} Advanced maternal age should be considered a factor for the prevention of uterine tony in elective CD. We suggest that guidelines for oxytocin administration should differentiate between young parturients and old parturients (age ≥35 years).

Data Sharing Statement

Data analyzed during this study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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