A Randomized Comparative Study of Pain Management: Oral Acetaminophen Versus Topical Lidocaine With/Without Epinephrine in Neonatal Circumcision

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Abstract

Introduction: The study assessed whether effective pain management of the neonate could be achieved with topical approaches rather than acetaminophen in circumcision. Epinephrine and/or lidocaine solutions with clinically proven safety were preferred for topical use.

Materials and Methods: This study was conducted by separating 105 neonates into three groups, each of which consisted of 35 patients. Group I was followed up and assessed by performing pain management using only acetaminophen; in Group II topical liquid local anesthetic medication without Epinephrine was used. In Group III topical liquid local anesthetic medication with epinephrine was used in pain management, including acetaminophen, to reduce oral medication if necessary. The pain was monitored using the Neonatal Infant Pain Scale.

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Results: In all three groups, it has been shown statistically that topical medication effectively relieves pain and reduces the need for oral medication. In the comparison of Group II and Group III, it was found that the presence of pain was lesser in the use of lidocaine containing epinephrine and less oral medication was required ($p<0.001$ & $p<0.001$). The frequency of topical application in Group II was statistically significantly lower compared to Group I ($p<0.001$). Topical administration containing epinephrine was more effective compared to the group using only oral acetaminophen or liquid lidocaine without epinephrine ($p<0.001$ & $p<0.001$).

Conclusion: Painless procedures should be preferred in surgical procedures of neonates. If painful procedures need to be performed, effective pain management plans should be set up beforehand. Few oral medications can be used in the management of pain in neonates. In surgical procedures such as circumcision, intensive medication use is required, topical pain-relieving medications can be used to avoid or reduce the need for drugs that may have adverse effects.

Keywords

- Circumcision
- Newborn
- Pain management
- Topical medications

Introduction

Our study is based on the hypothesis that the newborn feels pain and pain can be prevented with topical medication. Today, it is essential to minimize the pain during circumcision. The remarkable idea that the newborn does not suffer is based on the claim of Paul Emil Fleshing in 1872 that a baby's lack of myelin would prevent them from suffering pain[1]. Medical authorities accepted this viewpoint and caused surgical procedures to be performed without considering the importance of analgesia. Newborn circumcision is still performed without considering pain in some areas. However, contrary to this belief, it has been proven by measuring some physiological parameters that infants feel pain. It is now stated that newborns are

more sensitive than adults [2,3]. This study assesses the post-circumcision pain management, and aims to demonstrate that a painless period may be achieved with topical applications.

Materials and Methods

In the planning phase, it has been verified that use of topical lidocaine or epinephrine is safe. It has also been confirmed that information regarding epinephrine prolonging the desired effect, by preventing the active substance from moving away from the environment, is included in the literature [4]. It was determined that the parenteral (IO/IV) maximum dose of epinephrine specified as 1 mg, 0.01 mg/kg/dose, and could be used and repeated every 5-10 minutes. It was gauged that the maximum dosage would be reached in 80 repetitions with 1 ml applications, if they were mixed into systemic circulation. One of the findings was that epinephrine became rapidly inactivated in the body, did not accumulate, and did not have a prolonged impact [4]. Low concentrated 20 mg/ml Lidocaine™ solution (with or without 0.0125 mg/ml diluted epinephrine) was planned to use.

Based on the literature, the parenteral total maximum dose of lidocaine was 2400 mg/24h, and a 300 mg/dose could be used, and the maximum dosage would be reached in 120 repetitions with 1 ml applications, if they were mixed into the systemic circulation. Numerous publications have been cited suggesting that systemic absorption is negligibly low in topical use [4].

In our study, it was recommended to use 1 ml of liquid topical applications at 60-minute intervals and to use 10 mg/kg oral acetaminophen, a maximum of 4 times a day.

Infants, born after 37 weeks of gestation, with a bodyweight of 2,500- 3,500 grams and without any comorbid systemic disease, are included in the study.

A prospective, randomized, non-blind, non-placebo study was conducted in a single center. The study, which began with 216 patients, ended with the analysis of 105 patients. Participants were selected at random for an equal chance of allocation. For purposes of randomization, the admissions officer, who was not aware of any details concerning the study, was asked to spontaneously mark I, II, or III on the patient file **(Figure 1)**. The study was terminated in the group with 35 analyzed cases identified by the admissions officer. Patients who did not want to be included in the study, who did not perform the required

number of pain score analyses, and who were disconnected were not analyzed. Patients who did not give consent (n=27), and could not state that they could score pain accurately (n=54) were considered ineligible (n=81). As a requirement, the parent had to be present in the location of the procedure and be able to make up 1 ml of medicine.

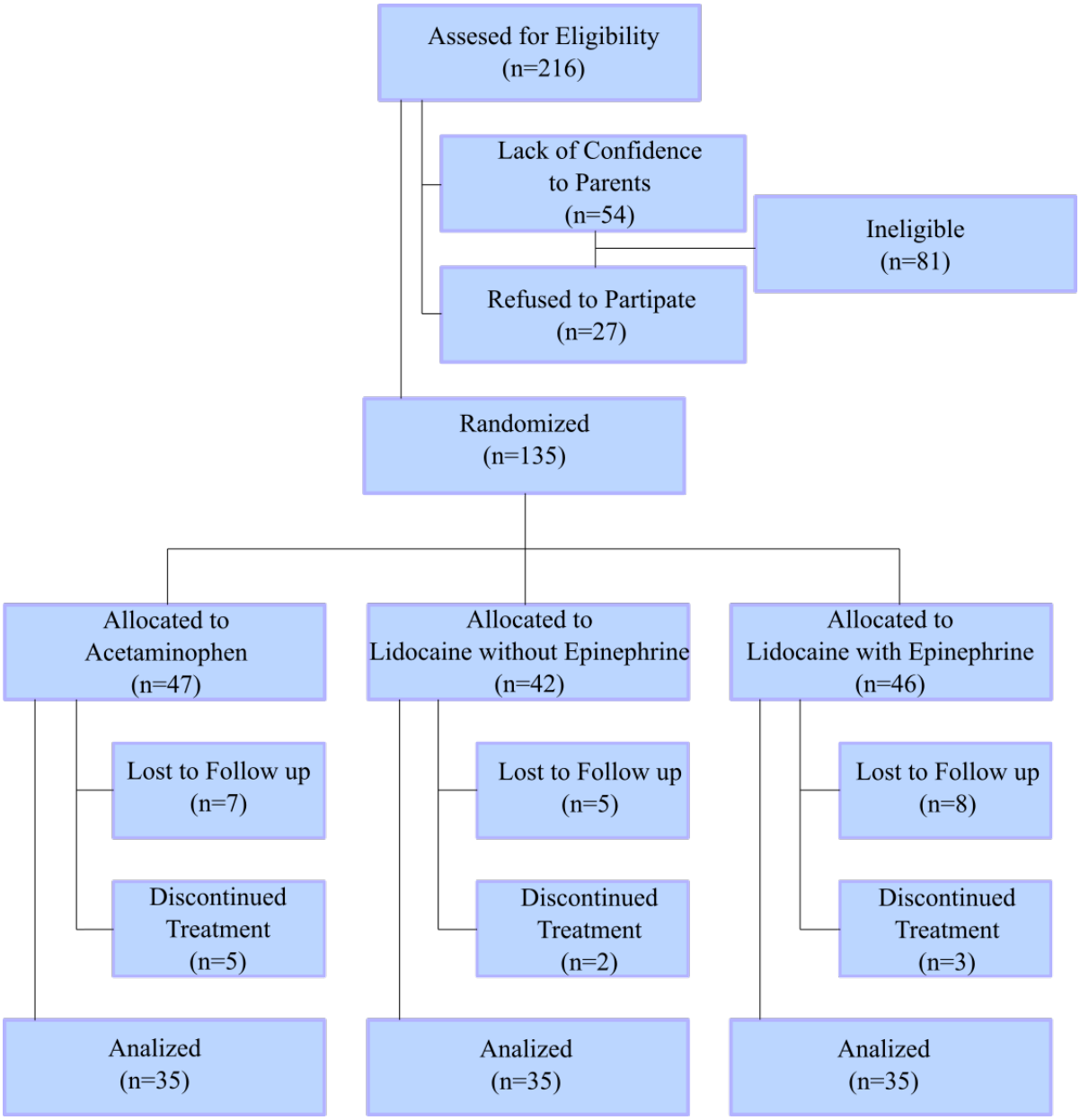

Figure 1: Flowchart

After receiving institutional research ethics board approval, the study was conducted on a total of 105 patients consisting of 3 groups of 35 newborns, between May 2021 and July 2021. Following verbal and written notification, and the overdose effects of medications were explained, informed consent was obtained.

It was planned to utilize infiltration anesthesia with lidocaine without epinephrine. Following the procedure, it was planned to continue with three separate groups. It was expected that the follow-up and recording of the received medications, the application, and the presence of pain should be commenced with infant nurses and continued with the parents. The neonatal infant pain scale (NIPS) was utilized and preferred for pain assessment. NIPS pain scoring was demonstrated to the parents before the procedure, pain levels were followed up after the procedure, and the administered or/and applied medications were recorded. According to the NIPS score system, values greater than 3 indicated pain. Parents were asked to obtain 6 separate pain scores within 24 hours. Cases with lower scores were considered as "lost".

As subcutaneous infiltration anesthesia, 3 injections, 0.2 ml each to the penis root at 2 and 10 o'clock for the dorsal nerve of the penis block, and 0.2 ml to the penoscrotal area for a deep branch of the perineal nerve block, and 0.6 ml of 20/ml epinephrine-free lidocaine were injected into all patients. Circumcision was performed after waiting for 5 min the following injection with dorsal slit method using absorbable suture material. The procedure was completed with a simple dressing.

Group 1: Control group. Following the procedure, no topical application was performed.

Group 2: 1 ml of 20mg/ml lidocaine alone was applied topically on the closed dressing to be repeated once an hour to the group.

Group 3: 1 ml of 20mg/ml lidocaine +0.0125 mg epinephrine was applied topically on the closed dressing to be repeated once an hour.

For all groups, 10 mg/kg. of acetaminophen PO 4 × 1 was prescribed. In Group I, the first dose was administered prior to the discharge of the newborn. The patients were discharged one hour after the procedure. After 48 hours, patients were called for a follow-up, and the records were examined.

Statistical analysis was performed using SPSS software 17.0. The comparisons among the variables of the groups that do not show a normal distribution were performed using the Mann-Whitney U-test. While comparisons among more than two groups were performed via the Kruskal-Wallis Test. The results were considered statistically significant at $p<0.05$.

Result

In Group 1, patients were followed up with oral acetaminophen, and a mean of 4.11 ± 0.68 pain was observed. They received painkillers on average 2.46 ± 0.61 times. When Group I was compared with Groups 2 and 3, it was determined that the presence of pain and the frequency of oral medication use were statistically significantly higher when compared with Group 2 and Group 3 ($p<0.001$ and $p<0.001$) **(Table 1).**

In group 2, patients were followed up with liquid topical lidocaine dressing without epinephrine, a mean of 2.43 ± 0.70 pain was observed. They received painkillers on average 1.43 ± 0.70 times. In the comparison of Group 2 and Group 3, it was found that the presence of pain was higher in the use of lidocaine containing epinephrine and much more oral medication was required. The frequency of topical application in Group 2 was statistically significantly higher compared to Group 3 ($p <0.001$ and $p <0.001$) **(Table 1).**

In Group 3, in which patients had liquid topical lidocaine dressing applied containing epinephrine, a mean of 1.14 ± 0.73 pain was observed. The patients received painkillers on average 0.60 ± 0.50 times. When group 3 was compared with Groups 1 and 2, it was determined that the need for oral acetaminophen was significantly lower ($p<0.001$). The presence of pain was significantly lower compared to Groups 1 and 2 ($p<0.001$) **(Table 1)**.

Table 1: Comparison of groups

		Mean±sd			p
		Group 1	Group 2	Group 3	
	Weeks	32,8±4	33,74±3	32,83±3	0,596
	Weight	3111,8±327	3160,86±312	3096,57±345	0,775
Number of	Pain	4,11±0,6	2,43±0,7	1,14±0,7	<0,001
	Doses	2,46±0,6	1,43±0,7	0,60±0,5	<0,001
	Applications	0	8,68±0,70	4.80±0,5	<0,05

It was determined that the frequency of topical medication use was significantly higher in Group 2 when compared with Group 3 ($p<0.05$). While the maximum number of applications in 24 hours was performed on 13 patients in group 2 with 10 repetitions, the minimum number of applications was performed on 12 patients in Group 3 with 4 repetitions **(Figure 2).**

Based on the analysis performed by the Kruskal Wallis Test, the use of oral painkillers was at the lowest level ($p<0.001$) and the frequency of feeling pain was significantly lower in group 3, in which epinephrine containing lidocaine was used ($p<0.001$) **(Table 2)**. It was shown in our study that the application had a statistically strong and significant positive effect in the group where topical liquid lidocaine application containing epinephrine was applied ($p<0.001$) **(Figure 2).**

Patient compliance was at 80% power and 92% confidence level (alpha=0.05) in post-op assessment.

Table 2: Comparison of groups

		Mean (±sd)		p
		Group 1	Group 2	
Number of	Pain	4,11±0,6	2,43±0,7	<0.001
	Dose	2,46±0,6	1,43±0,7	<0.001
		Group 1	Group 3	
	Pain	4,11±0,6	1,14±0,7	<0.001
	Dose	2,46±0,6	0,6±0,5	<0.001
		Group 2	Group 3	
	Pain	2,43±0,9	1,14±0,7	<0.001
	Dose	1,43±0,7	0,6±0,5	<0.001

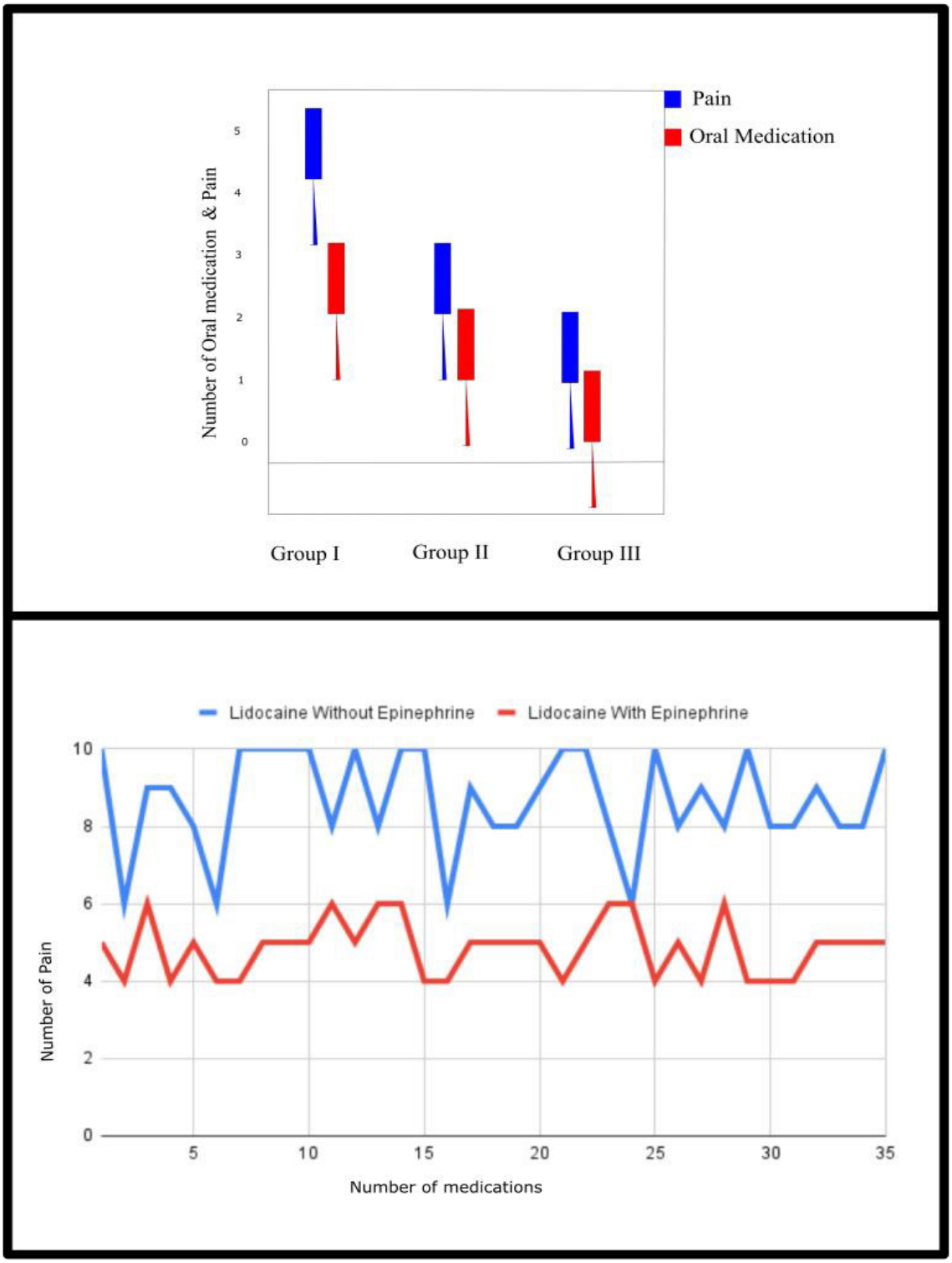

Figure 2: Pain & Medication Relations.

Discussion

The inability of newborns to express themselves, and difficulty in pain scoring urges practitioners to assess pain through secondary findings. An additional concern is that some medications are shown to be unreliable after a while, the use of drugs that are known to be safe in neonates should be reconsidered with suspicion [2-4].

Piñeiro-Carrero VM suggested that neonates are more sensitive to medication and require severe dose and drug adjustments. This is due to developmental changes in the metabolic activity of the liver from birth to adolescence, decreased capacity of the neonatal liver [5]. Albeit, there are many confusing studies related to the safe use of the widely-used drug acetaminophen. Brune, one of these researchers, remarks that hundreds of acetaminophen-related acute liver failures occur in developed countries. He underlines that acetaminophen is the most dangerous medicine in the world. Rose Cairns put forward the idea that acetaminophen continues to be used with the misconception that it is a safe medication. Its hepatotoxicity and adverse effects are underestimated, and stated that liver failure due to acetaminophen is gradually increasing. Brune and Steffen in their independent studies, Squires who examined 348 hepatic failures, suggested that the effects of acetaminophen on the failures are not less than 14% [6-9].

Taney. drew attention, Quentin Awori and Arana pointed out the lack of acetaminophen studies in early childhood and demonstrated inconsistencies in the studies. By analyzing available literature and dosage guidelines, a mismatch occurs between the current clinical use of acetaminophen and recommendations. This suggests using a cautious approach, particularly in extremely preterm neonates [10,11].

An ideal topical anesthetic medication should show minimal systemic absorption and high potency. Oni described it as "Topical lidocaine is a patient-friendly, noninvasive method of providing good analgesia for a variety of interventions". There are no restrictions on the over-the-counter sale of lidocaine and similar topical local anesthetics. This suggests that it might lead to excessive and uncontrolled use and significant problems related to this [2-4]. In his study examining the toxic effects, he revealed that when lidocaine is used together with epinephrine, the toxic dose limit is eliminated and systemic absorption is significantly reduced. Campbell and

Ameer suggested in their separate studies that topical use would not cause systemic side effects. Bryan demonstrated in an experimental study that even in abnormal skin structures, the systemic absorption of lidocaine is low and does not result in toxicity [12,13]. Burk underlined and Nestor assessed that lidocaine can be used safely. He remarked that no signs of risk were observed in clinical and laboratory evaluations [14,15].

There is negative information in textbooks about the use of epinephrine in the end organs. Krunic, who objected to the prohibition of parenteral use, stated that this prevailing view consisted of an erroneous dogma and suggested that epinephrine was not the primary reason in the reported cases of necrosis. Sylaidi who used lidocaine with adrenaline in a digital block demonstrated a temporary reduction in blood flow but no necrotic effect of the mixture. Moreover, Firoz revealed that necrosis would not occur in its parenteral use in finger anesthesia [16-18].

Gunaratne also showed in their series of 1260 cases that topical use of epinephrine did not have a significant systemic effect. Furthermore, Junior and Kuhar supported the use of topical epinephrine in different studies [19-21]. There have been huge groups that object to circumcision due to tissue loss, acute/chronic pain, and possible complications [22]. Despite this, its global popularity has not declined.

It has been demonstrated that non-pharmacological measures such as breast milk, sugared water, and massage have a positive impact on the infant in terms of newborn pain management. Note that publications raise strong doubts about the effectiveness of non-pharmacological measures. It might be noteworthy to consider medications that do not cause methemoglobinemia and do not have hepatotoxicity. The injection is an application that should be avoided since it is both a painful stimulus and a source of infection [2-4].

The study of Quentin Awori et al. supported our study and showed that follow-up after circumcision can be continued through topical applications. It has been shown that avoiding injection, which is one of the recommendations of AAP, is possible [12].

In our study, local anesthesia was utilized in all three groups by injecting lidocaine at 3 points, and the procedure was conducted painlessly. Following the procedure, early circumcision pain management continued via the administration of oral

acetaminophen, or application of topical lidocaine with/without Epinephrine. It was determined that acute pain following the procedure could easily be relieved in all three groups.

It has been recommended that painless procedures to be preferred in newborns. Less painful procedures should be selected wherever possible. As can be observed, the recommendations centered on pain. Acute pain due to circumcision is crucial and may cause acute or chronic, neurological, mental, and physiological trauma that could lead to behavioral changes in the infant. It has even been suggested that the release of free radicals, which are induced by acute pain, leads to cerebral damage.

Conclusion

There is no oral analgesic that is definitively demonstrated to be safe for the neonates. Dose reduction is vital since the safety margins of the most commonly used acetaminophen are uncertain. It is possible to reduce the dose of oral painkillers by using topical medications. Pain-free procedures should be preferred in the neonate. If pain is inevitable, injections that cause pain should be avoided or fewer chemical substances should be administered.

Ethical Consideration

This study received ethical code from the ethical committee of Istanbul medipol (E-10840098-772.02-1286).

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Conflict of interests

There is no conflict of interest

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