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Use of chloroprocaine in spinal anaesthesia - A comparative study of combination of chloroprocaine with fentanyl vs. chloroprocaine with nalbuphine for day care surgeries

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A B S T R A C T

Background: The subarachnoid block is a preferred regional modality for patients undergoing surgeries of below umbilical region. In this perspective, we aimed to compare the efficacy and safety of 40 mg intrathecal chloroprocaine1% alone versus in combination with nalbuphine 0.8mg and fentanyl 20 µg as an adjuvant in day care surgeries performed under subarachnoid block.

Method: Overall, 150 patients were enrolled in this research. They were randomly divided into three groups of 50 each with the help of computer-generated random tables. Both the patient and the observer were blinded to the study. Group C, NC and FC received 40mg of 1% chloroprocaine (4ml) with 1 ml normal saline, nalbuphine 0.8 mg in 1 ml, fentanyl 20µg in 1 ml intrathecally respectively.

Result: The time of onset of sensory block was calculated when sensory block was achieved at the level L1. No significant difference was observed between groups in onset of sensory block, peak sensory block level and time to reach peak sensory block level.

The time for two-segment regression and regression to S2 was statistically significant between groups as the mean time was fastest in group C followed by group FC and NC. The VAS score was greater in control group as compared to group FC and NC at 120 minutes.

Conclusion: Thus, we conclude that addition of opioids as an adjuvant to intrathecal short acting local anesthetic 1% chloroprocaine have synergistic effect on analgesic action without affecting motor block.

Keywords: Spinal anesthesia, Chloroprocaine, opioids, fentanyl, nalbuphine.

INTRODUCTION

Chloroprocaine is an ester class local anesthetic with a potentially favorable profile for short procedures and is indicated for neuraxial anesthesia. Chloroprocaine with sodium bisulfite as preservative came into clinical practice in 1952. Soon patients started to develop nerve injury during epidural anesthesia due to its preservative and 2%~3% concentration of chloroprocaine [1-2]. Hence, by early 1980's it was discontinued from the market. Chloroprocaine was reintroduced in a preservative free formulation as 1% solution and brought upon a revolutionary change in ambulatory surgeries [3]. Post-operative pain is of major concern with intrathecal use of short-acting local anesthetic agents. Adjuvant can be added to local anesthetic agents to prolong the duration of analgesia. Fentanyl, is primarily a µ-opioid agonist and Nalbuphine is

an agonist-antagonist opioid gets bound to μ-receptors, in addition to K (kappa) and δ (delta) receptors. This results in prolonged analgesia with a decreased need for rescue analgesics.
In this study, we aimed to compare the efficacy and safety of 40 mg intrathecal chloroprocaine1% alone versus in combination with nalbuphine 0.8mg and fentanyl 20 μg as an adjuvant in daycare surgeries performed under subarachnoid block and to study the onset, duration and time to complete regression of sensory and motor blockade. We also studied the occurrence of complications like hypotension, bradycardia, respiratory depression, nausea, vomiting, pruritus, and urinary retention.

METHODOLOGY

The research was performed from January 2020 to August 2021 as prospective randomized double blinded comparative study and was conducted at Mahatma Gandhi Hospital attached and affiliated to Mahatma Gandhi University of Medical Science and Technology, Jaipur, Rajasthan, India. An approval was obtained from the institutional ethics committee. The research was prospectively registered with Clinical Trial Registry India (www.ctri.nic.in: CTRI/2021/06/034464).

All patients who fulfilled the inclusion criteria were assessed by a thorough preanesthetic evaluation and reviewed on the day of surgery. Informed written consent was obtained from all patients. Overall, 150 patients were enrolled in this research. They were randomly divided into three groups of 50 each with the help of computer-generated random tables [Figure 1]. Both the patient and the observer were blinded to the study. Group C, NC and FC received 40mg of 1% chloroprocaine (4ml) with 1 ml normal saline, nalbuphine 0.8 mg in 1 ml, fentanyl 20μg in 1 ml intrathecally respectively.

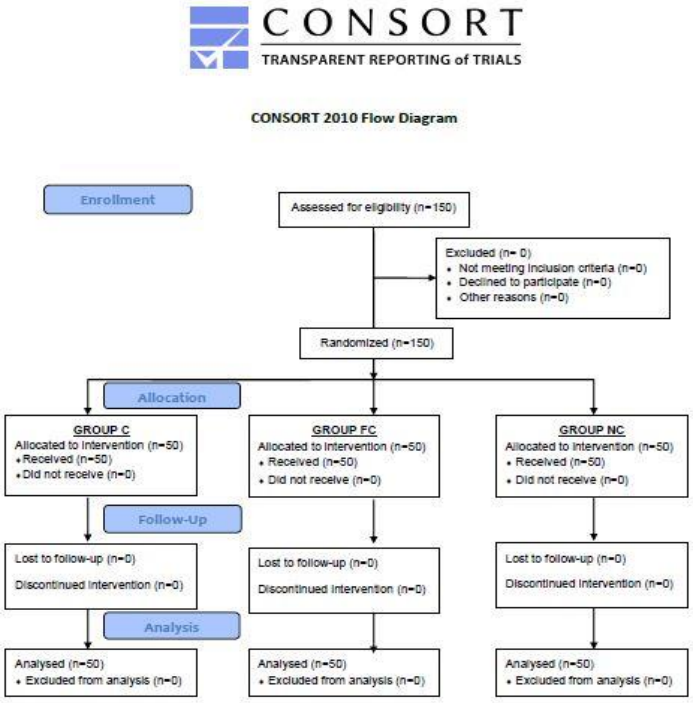


Figure 1: CONSORT 2010 diagram

The study drugs were provided in prefilled syringe having identical volumes of 5ml each. All patients were premedicated with tablet alprazolam 0.25 mg on the night before surgery. A fasting status of 8 to 10 hours was ensured. In the operating room, intravenous line was secured and co-loading was done with 10 ml/kg injection ringer lactate solution. Standard monitoring such as ECG, NIBP and SpO_2 were applied and monitored.

Patients were placed in sitting position and 2 ml of local anesthetic agent 2% xylocaine was injected in subcutaneous tissues at L_3-L_4 level under all aseptic precautions. Subsequently, subarachnoid block was performed using 25-gauge Quincke's needle and after confirming free & clear flow of cerebrospinal fluid, study drugs were injected. Immediately thereafter the patients were placed in supine position. Injection midazolam 1 mg was administered intravenouslyin every

patient as anxiolytic. Patients were evaluated for sensory and motor block, intra and postoperative hemodynamic and side effects at frequent intervals.

Sensory block was assessed using pinprick method via 25 g hypodermic needle every 2 min until highest dermatomal level was reached and every 15 minutes till regression to S_2 dermatome. Onset of sensory block (achieved at the level $L_{1)}$, time to achieve the highest dermatomal level, and time to sensory block regression to S_2 level (duration of sensory block) were recorded.
Motor block parameters were evaluated using modified Bromage scale as onset of motor block (Bromage 1), time to reach maximum motor block (Bromage 4) were all noted. All the parameters were evaluated and recorded from the time of subarachnoid injection at an interval of every two minutes till highest level motor block was achieved and then every fifteen minutes till the complete regression of motor block.
Pain was assessed using 10-point visual analogue scale every 30 minutes in the post anesthesia care unit. In case of pain, rescue analgesia (injection tramadol 100 mg in 100 ml 0.9% normal saline) was administered intravenouslyto the patients.

Sedation was also assessed from intrathecal injection to 120 minutes at every 30 minutes interval using Ramsay sedation score. Side effects such as hypotension, bradycardia, shivering, respiratory depression, nausea, vomiting and pruritus were noted during intra-operative and postoperative period.

We made use of modified Aldrete score for discharge criteria from post anesthesia care unit. Patients were shifted to their respective admission wards after achieving a modified Aldrete score ≥ 9. Patients were given discharge from the hospital after "post anaesthesia discharge score" (PAD Score) criterion was met. Patients with PAD Score ≥ 9 were regarded as fit for discharge from hospital and time of discharge from the hospital was noted.

This size was calculated to detect a difference in onset, duration and time to complete regression of sensory and motor blockade between the groups and was based on pair-wise 2-sided Mann-Whitney U tests. An overall type I error of 5% with a Bonferroni correction, we used an α level of 1.667% per pair-wise comparison.
For statistical analysis we entered the data in Microsoft excel spreadsheet 2010 version and then analyzed it by statistical software **IBM SPSS®** (version 28.0). Data was analyzed in form of mean and standard deviation for arithmetical variables and percentage for qualitative data. Unpaired student t-test was applied for a difference in mean involved unpaired samples. One-way analysis of variance (**one-way ANOVA**) was used to compare means of three samples for numerical data (using the F distribution). A **chi-square test** ($\chi 2$ test) was used for analysis of qualitative data.

If the calculated *p*-value came out to be below the threshold chosen for statistical significance (0.05) then the null hypothesis was rejected in favor of the alternative hypothesis. Hence, P-value ≤ 0.05 was considered statistically significant.

ABBREVIATIONS:

PONV	Post operative nausea &vomiting
PDPH	Post dural puncture headache
TNS	Transient neurologicalsymptoms
ASA	American Society of Anesthesiologists
NIBP	Noninvasive blood pressure
SpO_2	Peripheral arterial oxygen saturation
IV	Intravenous
PACU	Post anaesthesia care unit
HR	Heart rate
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
cm	Centimeter
Kg	Kilogram
mg	Milligram
µg	Microgram
min	Minute

ml Milliliter
CNS Central nervous system
CVS Cardiovascular system
SD Standard deviation

Observation Tables

Table 1: Demographic variables

Variable	Group C	Group FC	Group NC	P -Value
Age in Year	46.06 ± 10.08	40.42 ± 11.01	39.50 ± 10.37	0.90
Male **Female**	35 15	35 15	34 16	0.96
Weight	70.38 ± 11.05	67.25 ± 08.89	68.53 ± 6.65	0.22
Height	1.70±0.09	1.70 ± 0.07	1.68±0.04	0.42
BMI	24.03 ± 2.00	23.16 ± 2.00	24.02 ± 2.00	0.42
Duration of surgery	36.00 ± 10.00	34.00 ± 09.00	38.00 ± 10.00	0.17

Table 2: Characteristics of sensory and motor block and clinical data.

Characteristic (Time in Minutes)	Group C	Group FC	Group NC	P -Value
Onset of sensory block (Level L_1) (in Seconds)	72.00±33.26	69.00±19.41	63.00±30.03	0.36
Peak sensory block level	T_5	T_4	T_4	0.68
Time to reach peak sensory block level	17±6	19±5	18±6	0.37
Time for two segment regression	50.76±9.73	66.70±9.36	74.12±9.91	<0.001*
Time for regression to S_2	147.28±13.85	156.06±14.73	202.40±31.57	<0.001*
Onset of motor block	2.6±1.45	3.1±1.61	3.3±1.65	0.18
Time to reach peak motor block	4.9±3.3	5.6±3.6	5.9±3.8	0.15
Duration of motor block	77.40±11.73	78.02±11.85	78.86±11.91	0.82
Duration of stay in PACU	47.93±7.91	47.20±10.65	47.53±8.16	0.97
Time for first void	177.46±33.41	177.78±38.42	189.95±26.07	0.10
Time for first rescue analgesia	148.16±12.64	159.23±12.64	210.38±10.04	<0.001*
Time for unassisted ambulation	154.10±24.17	156.34±24.83	157.55±24.54	0.43
Time for readiness to discharge from hospital	202.64±32.59	205.68±36.74	213.34±30.03	0.15

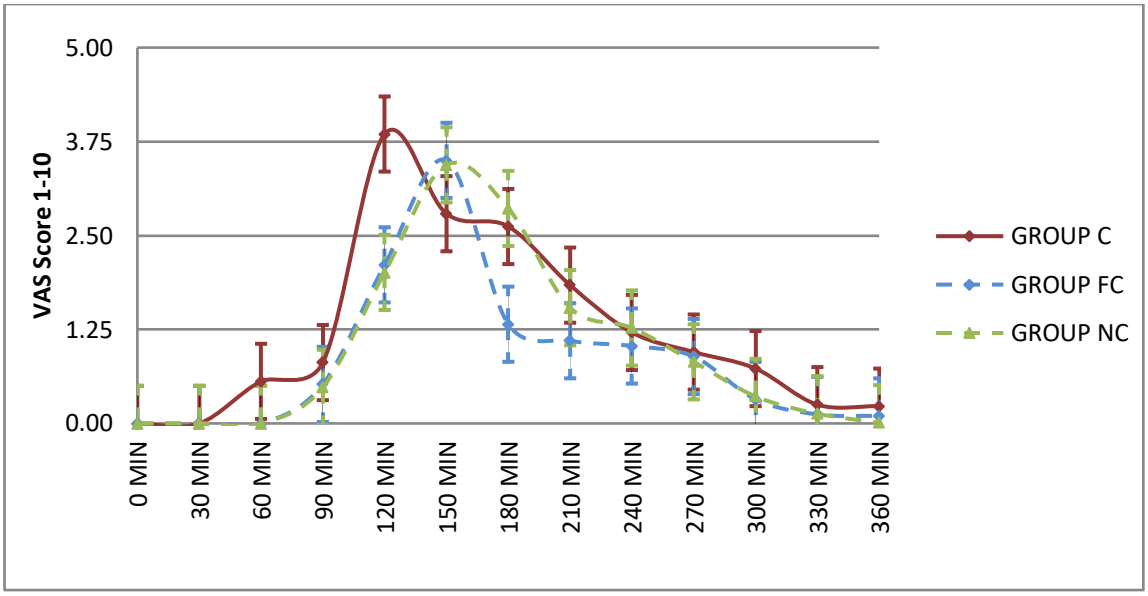
PACU = post anesthesia care unit

Table 3: Perioperativecomplications

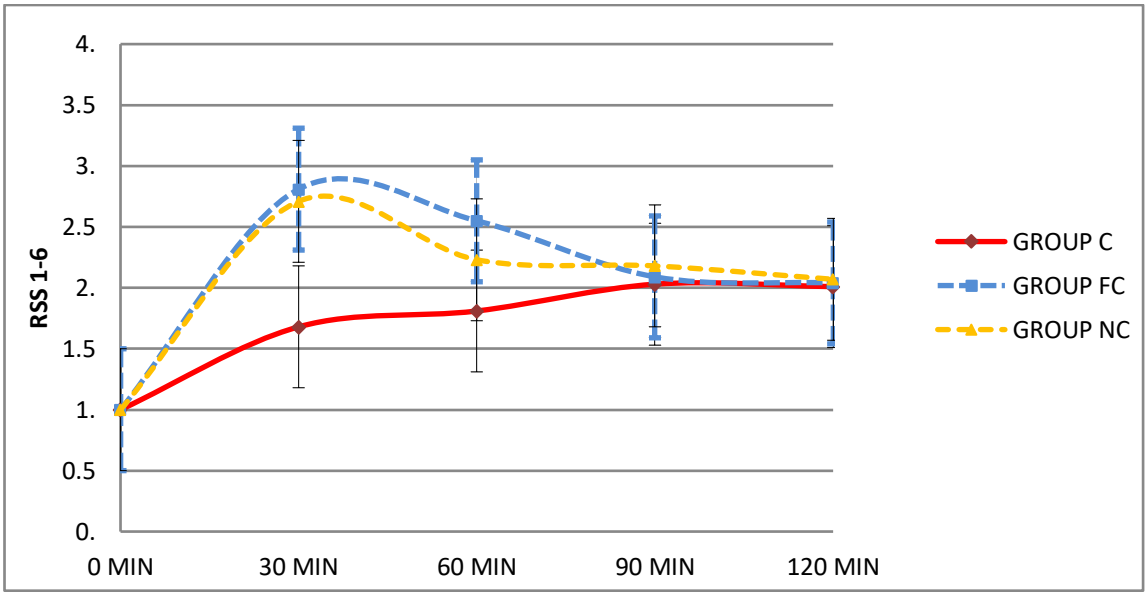
Side Effects	Group C *(n=50)*	Group FC *(n=50)*	Group NC *(n=50)*
Bradycardia	0	1	0
Hypotension	0	0	1
PONV	0	2	4
PDPH	1	0	0
Pruritus	0	1	2
TNS	0	0	0

Values are in absolute number PONV = postoperative nausea and vomiting, PDPH = postdural puncture headache, TNS = transient neurological symptoms

Graph 1: Visual analogue scale



Graph 2: Ramsay Sedation Score



RESULTS

150 patients aged 18 to 65 years were studied: 69% were male and 31% female. The anthropometric parameters in terms of age, sex, weight, height, BMI, and duration of surgery were comparable in all four groups with P > 0.05 [Table 1]

Association of type of surgery in all the groups was not statistically significant (P = 0.35). The time of onset of sensory block was calculated when sensory block was achieved at the level L_1. No significant difference was observed between groups in onset of sensory block (p value >0.05). The intergroup comparison was comparable between group (FC and NC) and group (FC and C). However, the data was statistically significant among group NC and group C (P value = 0.013). No significant difference was observed in peak sensory block level and time to reach peak sensory block level. The maximum number of patients achieved T_8 level in both groups (32% and 24% in group FC and group C respectively) while T_6 in group NC (28%). [Table 2]

The time for two-segment regression and regression to S_2 was statistically significant between groupsas the mean time was fastest in group C followed by group FC and NC ($P < 0.05$). The intergroup comparison was also statistically significant between the three groups.

In our study the onset, time to reach peak motor block, the duration of motor block was statistically comparable between groups ($P > 0.05$). [Table 2]

The VAS score was greater in control group as compared to group FC and NC at 120 minutes ($P < 0.05$) [Graph 1]. The time for the first rescue analgesia was significantly earlier in group C as compared to group NC and FC ($P < 0.05$). However, there was no difference between group FC and NC. [Table 2]

The RSS was higher in group FC and NC as compared to control group at 30 min and 60 min ($P < 0.05$). However, the overall score was < 3 hence the sedation was mild only. [Graph 2]
In our study side effects like bradycardia, hypotension, PONV, PDPH, pruritus, and TNS were comparable in all three groups.

No significant difference was observed between groups in terms of mean arterial pressure, SpO_2,PACUstay, time to first void and the time for unassisted ambulation or discharge from the hospital.

DISCUSSION

Daycare surgeries are considered advantageous in modern practice as they reduce the health care cost and burden on health care system. Moreover, this is an era of safe surgical and anesthesia practices. This poses a great challenge to anesthetists because early and complete recovery is desirable besides safety concerns. After the reinvent of chloroprocaine, subarachnoid block has emerged as a possibility for below umbilical out-patient surgeries.

Our study exemplifies the use of chloroprocaine in spinal anesthesia in covenant with the study which concluded that intrathecal dose of 35-40 mg chloroprocaine (10 mg/ml) provides consistent sensory and motor block for day care surgery and resulted in early ambulation [4].

Addition of opioid adjuvants like nalbuphine and fentanyl augment sensory blockade with minimal to no effect on motor blockade. Opioids exert analgesic action via mu, delta and kappa-receptors located in cortical areas and the substantia gelatinosa in spinal cord [5].

In our study, the onset time of sensory blockade was earlier in both the opioid adjuvant groups as observed in study comparing intrathecal buprenorphine versus chloroprocaine (2.93±0.94 minutes and 3.11±1.53 minutes) respectively. (P=0.507) [6]. Some researchers studied the effect of 40 mg intrathecal chloroprocaine with fentanyl 12.5 µg and observed that mean time to achieve peak sensory block in chloroprocaine group was 20 minutes and the mean peak sensory block level was T_7-T_8 in both the groups which was comparable with our results [7]. The time for two segment regression and regression to S_2 in our study was comparable with a study published on intrathecal chloroprocaine 40 mg with fentanyl 20 µg which resulted in two segment regression in 77 ± 7 minutes and time to complete regression of sensory block at 104±7 minutes. They also observed that it does not increase time of motor blockade [8].

As per our observations, the addition of intrathecal opioid adjuvant did not bring about any significant change in onset time of motor block and the literature also suggests the same. In a study comparing different doses of intrathecal opioid adjuvants with local anesthetic do not affect the duration of motor blockade (125.33 ± 5.71, 125.87 ± 20.17 minutes respectively. P=0.890) and were statistically insignificant among all groups [9-10].

The opioid and benzodiazepine induced sedation makes it vital to monitor the sedation level of the patient and also helps us to access the analgesic effect of the study drug. The observations in our study correlates with the one made by author Bindra TK. et al in his study of postoperative analgesic effect of intrathecal nalbuphine vs. intrathecal fentanyl in cesarean section and concluded that the mean duration of effective analgesia was 259.20 ± 23.23 minutes in (nalbuphine 0.8mg) group I, 232.70 ± 13.15 minutes in (fentanyl 20 µg) Group II, and 168.28 ± 7.55 minutes in (normal saline) Group III. However RSS scores were less than three [11]. These findings direct towards the fact that intrathecal opioid leads to mild sedation.

The sensory blockade weans off in due time after the surgery and patient start to experience post-surgical pain. In our study, we chose to administer inj. tramadol 100 mg i/v in 100ml 0.9% normal saline. Inj. ondansetron 0.1 mg/kg was administered prior to tramadol injection to overcome its emetic action on $5HT_3$ serotonin receptor in brain cortex. Also, it might prove useful in patients in whom non-steroidal anti-inflammatory (NSAID) are not recommended or need to be used with caution.

In a study published by Gurunath BB et al. [12] stated that postoperative analgesic efficacy of intrathecal nalbuphine when compared to fentanyl with bupivacaine was notably superior. Our results correspond to above mentioned studies and further conclude that 0.8 mg dose of intrathecal nalbuphine has much better results than 20 µg dose of intrathecal fentanyl.

Our study corroborates with study done by Camponovo C et al.indicating that the mean time to ambulation with chloroprocaine was 154.10 ± 24.17 minutes in 50 subjects [13]. This could also be due to the study design and the sample size of our study.

Urinary retention, early ambulation, void, and minimum to negligible side effects, every single one contribute to shorter length of hospital stay in day care surgeries.

In a previous study the mean time to void in chloroprocaine-fentanyl group was 104±7 minutes while it was 95±9 minutes in chloroprocaine-saline group. All subjects were able to successfully void in both groups [8]. The observations made in our study correlates with the studies published earlier. The use of intrathecal chloroprocaine results in early voiding which favors its use in day care surgery and catheterization was not done in any of the patients as none of the subjects complained of urinary retention.

Bhaskara et al conducted a prospective, randomized, comparative study among 60 patients under spinal anesthesia with intrathecal 30 mg chloroprocaine with 12.5 µg fentanyl (Group C) and 1.5 ml of 0.5% ropivacaine with 12.5 µg fentanyl (Group R). The patients enrolled in chloroprocaine group had an early discharge from hospital or in other words significantly less hospital stay (176.72±12.22 minutes) than ropivacaine group (294.36±25.71 minutes) [14].

In our study, time to early ambulation, early void has led to shorter length of hospital stay i.e. early discharge from the hospital. None of the patients had any surgical complication which could also have led to longer stay at the hospital.
One patient in fentanyl group had transient bradycardia which spontaneously resolved without any medication. One patient in nalbuphine group had transient hypotension which resolved with intravenous fluid administration. Two patients in fentanyl group while four patients in nalbuphine group suffered post-operative nausea and vomiting which resolved with intravenous injection of ondansetron (0.1 mg/kg). It happened after administration of injection tramadol as rescue analgesia and could have been due to its $5HT_3$ reuptake inhibitory action. One patient in chloroprocaine group had post dural puncture headache which resolved after adequate fluid intake.

One patient in fentanyl group and two patients in nalbuphine group complained of mild pruritus for which no medication was administered and it resolved spontaneously as the block regressed to S_2. Mulroy et al. [15] published a study on intrathecal use of fentanyl with local anesthetic agent prilocaine, lidocaine and bupivacaine. The incidence and severity of pruritus was less in our study that indicates that intrathecal fentanyl and nalbuphine causes less pruritus when combined with local anesthetic chloroprocaine.

After discharge from hospital patients were telephonically followed up for to enquire about side effects like post dural puncture headache, and transient neurological symptoms. Transient neurological symptoms were not observed our study from the time of intrathecal injection till 1 week follow up done telephonically in all our patients.

CONCLUSION

Thus, we conclude that addition of opioids as an adjuvant to intrathecal short acting local anesthetic 1% chloroprocaine have synergistic effect on analgesic action without affecting motor block and nalbuphine is better than fentanyl as adjuvant to chloroprocaine when administered intrathecally for day care surgeries performed under subarachnoid block.

LIMITATIONS

A single tertiary center study was a key limitation of our study.

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- **Conflict of interest:** No potential conflict of interest relevant to this article was reported.
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