

## DEXMEDETOMIDINE VERSUS CLONIDINE AS AN ADJUVANTS TO BUPIVACAINE IN LOWER LIMB SURGERIES

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## Abstract

**Background:** Dexmedetomidine is a recently developed pharmaceutical compound that exhibits a high degree of selectivity as an agonist for the alpha 2 adrenergic receptors. The alpha 2/alpha 1 selectivity ratio of this compound is eight times greater than that of clonidine. The primary objective of this study is to assess the effectiveness of intrathecal clonidine and dexmedetomidine as supplementary agents to bupivacaine in improving intraoperative and postoperative pain relief and maintaining stable hemodynamics. **Materials and Methods:** Total 90 patients were randomly divided into three groups of 30 each Group A: 0.5% bupivacaine 15 mg + 0.5 ml normal saline Group B: 0.5% bupivacaine 15 mg + 50 µg clonidine Group C: 0.5% bupivacaine 15 mg + 5 µg dexmedetomidine. Onset and duration of sensory block and motor block, the highest level of sensory blockade, and the duration of analgesia were assessed. **Results:** The maximum level of sensory block attained varied among the groups, with group A reaching T4, group B reaching T5, and group C reaching T6. The mean time taken for regression of sensory block by two segments was significantly shorter in group A compared to groups B and C. The mean time taken for maximum sensory blockade was significantly shorter in group A compared to groups B and C. **Conclusion:** Intrathecal dexmedetomidine supplementation of the spinal block seems to be a good alternative to intrathecal magnesium sulfate, as it produces earlier onset and prolonged duration of sensory and motor block without significant hemodynamic alterations. Dexmedetomidine and clonidine added as adjuvants to intrathecal bupivacaine were found to be effective in elective lower limb surgeries, with respect to block characteristics, hemodynamic changes, and adverse effects.

## INTRODUCTION

Regional anaesthesia is the technique of choice for the majority of lower abdomen and lower limb operations. It permits the patient to remain cognizant and minimises or eliminates the problem of airway management.<sup>[1]</sup> For decades, lignocaine was the most popular local anaesthetic for spinal anaesthesia.<sup>[2,3]</sup> Bupivacaine is three to four times more potent and has a lengthier duration of action than lignocaine. Slow onset of action and decreased motor block are disadvantages. In India, 0.5% hyperbaric bupivacaine is widely used for spinal anaesthesia. However, it does not induce prolonged postoperative analgesia. Therefore, an adjuvant is required for extending postoperative analgesia. Soon after the discovery of opioid receptors and endorphins in the spinal and two supraspinal regions, spinal analgesics were utilised.

The first opioid administered intrathecally to augment neuraxial blocks was morphine.<sup>[4,5]</sup> Morphine can cause severe adverse effects, including delayed and erratic respiratory depression, postoperative nausea and vomiting, pruritus, and urinary retention.<sup>[6,7]</sup> Due to their sedative, analgesic, and hemodynamic stabilising effects, -2 adrenoceptor agonists have recently been used as adjuvants to local anaesthetic agents.<sup>[8,9]</sup> The actions of the -2 adrenergic agonist clonidine are diverse. Clonidine was administered orally to prolong spinal anaesthesia. Adding intrathecal clonidine to bupivacaine prolongs analgesia and reduces postoperative morphine consumption. Clonidine has antihypertensive properties and can enhance the local anaesthetics' effects.<sup>[10,11]</sup> Clonidine has been shown to prolong the sensory blockade, motor blockage and decrease the volume or concentration of local

anaesthetic necessary to induce post-operative analgesia. Large doses of intrathecal clonidine (up to 450g) without local anaesthetics provide sedation and potent and long-lasting postoperative analgesia, but are insufficient for surgical anaesthesia; for this reason, clonidine has been used as an adjuvant to local anaesthetics rather than alone.<sup>[9]</sup> Also a -2 adrenergic agonist, dexmedetomidine is pharmacologically related to clonidine and is the most recent agent in this class to be approved by the FDA for use in humans as a short-term medication (24 hours) for analgesia and anaesthesia in intensive care units in 1999.<sup>[12]</sup> Its distinctive properties make it appropriate for sedative and analgesia throughout the entire perioperative period. Dexmedetomidine intravenously reduces the hemodynamic response to laryngoscopy and intubation, according to multiple studies.<sup>[13]</sup> Dexmedetomidine is an alpha- 2 adrenoceptor agonist with eightfold greater affinity for alpha- 2 adrenoceptors than clonidine. Compared to clonidine, the ratio of alpha- 1: alpha- 2 receptor binding selectivity for dexmedetomidine is 1:1620.<sup>[13]</sup> While clonidine has been used successfully as an adjunct to local anaesthetic agents for intrathecal administration, there are only a few studies available for dexmedetomidine. In order to evaluate and compare the efficacy of clonidine and dexmedetomidine as adjuvants to intrathecal hyperbaric 0.5% bupivacaine in patients scheduled for elective lower limb surgery, this study has been conducted.<sup>[14]</sup>

#### **Aim of the Study**

To evaluate and compare the efficacy of dexmedetomidine and clonidine added as adjuvants to 0.5% hyperbaric bupivacaine administered intrathecally for elective lower limb surgeries.

## **MATERIALS AND METHODS**

Study design: Comparative observational study

Sample size: 90 patients

Method of sampling: Random sampling

Analytical statistics: Chi-square test

#### **Inclusion Criteria**

- Patients between the ages of 18 and 60
- ASA I and II is scheduled to undergo elective lower limb procedures.

#### **Exclusion Criteria**

- Regional anaesthesia or patient refusal.
- A body mass in excess of 120 kg
- After spinal operations, spinal deformity
- Patients with disease such as coagulopathy heart, neurological disorder, liver, or kidney disease
- History of drug hypersensitivity
- Pregnancy

Ninety patients between the ages of 18 and 60 belonging to ASA physical status I and II and scheduled for elective lower limb surgery were randomly divided into three groups (n=30) after receiving approval from the institutional ethics committee. Randomization was conducted using the technique of sealed envelopes. Group A (the control group) was administered 15 mg of 0.5% hyperbaric bupivacaine and 0.5 ml of normal saline. Group B (Clonidine group) was administered 15mg of 0.5% hyperbaric bupivacaine along with 50g clonidine. Group C (Dexmedetomidine group) received 15 mg of 0.5% hyperbaric bupivacaine in conjunction with 5g dexmedetomidine. In all three groups, the total volume of the injected solution was 3.5ml.

Preoperative planning: Each patient underwent a preoperative evaluation, and written consent is obtained. Before surgery, patients were denied sustenance for 6 hours and clear fluids for 2 hours. The night before surgery, all patients were premedicated with Ranitidine 150 mg and Alprazolam 0.5 mg tablets. Half an hour before anaesthesia, the intravenous line was secured with an 18-gauge cannula and preloaded with 500 ml of Ringer lactate solution. In the operating room, appropriate airway management apparatus and emergency medications were kept on hand. Checking the horizontal position of the operating table. The patients were moved and positioned in the operating chamber. The patient's noninvasive blood pressure monitor, pulse oximeter, and ECG leads were connected. Systolic and diastolic baseline blood pressure, mean arterial pressure, pulse rate, respiratory rate, and oxygen saturation were recorded prior to surgery. Intraoperative monitoring in a seated position, the back skin was treated with an antiseptic solution and covered with a sterile cloth. Under aseptic precautions, a subarachnoid block was performed at the L3-L4 level via a midline approach with a 25G Quincke spinal needle, and the study medication was injected while the operative table was kept flat. Patients were immediately instructed to rest supine, and the time of injection of the study drug was recorded.

#### **Statistical Analysis**

The collected data was analysed statistically using the SPSS trial version. The results were presented as the range, the mean, and the standard deviations. A one-way analysis of variance (ANOVA) was utilized to compare normally distributed continuous variables between groups. Comparing nominal categorical data between study groups using the chi-square or Fisher's exact test. Using the Mann-Whitney U-test, ordinal categorical variables and non-normal distribution continuous variables were compared. A 'p' value of 0.05 was deemed statistically significant.

## RESULTS

**Table 1: Baseline characteristics of study participants**

Characteristics	Group A	Group B	Group C	p value
Age	31.22 ± 5.67	33.36 ± 4.23	32.61 ± 6.74	0.43
Gender				
– Male	15 (50.0%)	17 (56.7%)	16 (53.3%)	0.87
– Female	15 (50.0%)	13 (43.3%)	14 (46.7%)	
Height (cm)	159.42 ± 4.73	161.01 ± 6.18	161.62 ± 5.14	0.76
Weight (kg)	60.95 ± 4.66	61.37 ± 5.58	60.78 ± 5.74	0.97

Basic characteristics such as age, gender, height, and weight were not significantly different between three groups (Table 1).

In group A (the control group), the average onset of sensory blockade is 2.82 minutes, whereas in group B (the clonidine group) it is 1.45 minutes and in group C (the dexmedetomidine group) it is 1.17 minutes. There is a highly significant statistical difference between group A and groups B and C ( $p < 0.0001$ ), and there is a statistically significant difference between group B and group C ( $p = 0.024$ ) (Table 2).

Maximum sensory blockade attained in T4 level of sensory blockade was higher in group C (the dexmedetomidine group: 40.0% -12/30) than group A (the control group: 6.7% -2/30) and group B (the clonidine group: 26.6% - 8/30). However significant difference was observed only between group A and group C ( $p = 0.009$ ). p value between group A and Group B was 0.086 and between group B and Group C was 0.347 (Table 2).

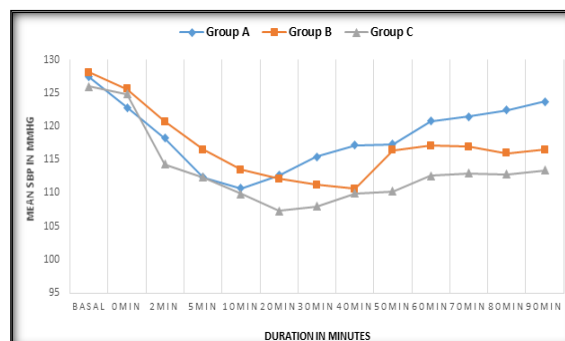
The average time required to achieve maximal sensory blockade is 7.41 minutes in group A (the control group), 5.91 minutes in group B (the clonidine group), and 5.23 minutes in group C (the dexmedetomidine group). There is a highly significant statistical difference among group A versus groups B ( $p < 0.001$ ) and group A versus group C ( $p < 0.001$ ). There is a statistically significant difference between group B and group C ( $p = 0.001$ ) (Table 2).

**Table 2: Comparison of sensory block and Duration of analgesia between three groups**

Characteristics	Group A	Group B	Group C	p value
Sensory onset (min)				
Mean ± SD	2.82 ± 0.64	1.45 ± 0.54	1.17 ± 0.39	A v/s B - < 0.0001
Range	2-4	1-2	1-2	A v/s C - < 0.0001 B v/s C - 0.024
Maximum level of sensory block attained				
T4	2 (6.7%)	8 (26.6%)	12 (40.0%)	A v/s B - 0.086
T5	4 (13.3%)	5 (16.7%)	2 (6.7%)	A v/s C - 0.009
T6	24 (80.0%)	17 (56.7%)	16 (53.3%)	B v/s C - 0.347
Time taken for maximum sensory block (min)				
Mean ± SD	7.41 ± 1.12	5.91 ± 0.83	5.23 ± 0.71	A v/s B - < 0.001
Range	6-9	5-7	4-7	A v/s C - < 0.001 B v/s C - 0.001
Time taken for two segment sensory regression (min)				
Mean ± SD	79.49 ± 10.17	136.38 ± 10.96	136.35 ± 11.67	A v/s B - < 0.001
Range	60-95	120-155	120-150	A v/s C - < 0.001 B v/s C - 1.00
Duration of analgesia in (min)				
Mean ± SD	191.23 ± 22.94	342.33 ± 28.12	369.33 ± 34.13	A v/s B - < 0.001
Range	150-240	300-390	300-420	A v/s C - < 0.001 B v/s C - 0.001

In group A (the control group), regression of sensory block by two segments takes an average of 79.49 minutes, whereas it takes 136.38 minutes in group B (the clonidine group). 136.35 minutes in the dexmedetomidine cohort (group C). There is a statistically significant distinction between groups A and B and between groups A and C ( $p < 0.0001$ ). However, there is no significant statistical difference between groups B and C ( $p = 1.00$ ) (Table 2).

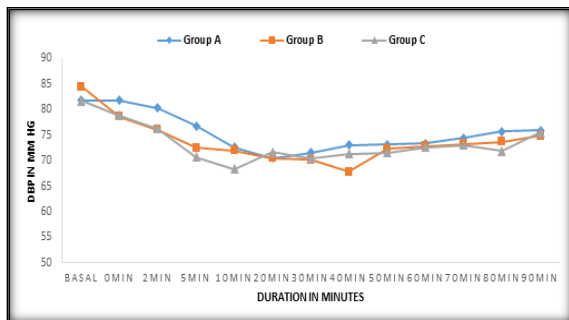
The duration of analgesia was significantly higher in in group C (369.33 minutes) and in group B (342.33 minutes) as compared to group A (191.23 minutes) as shown in table 2. This difference in duration of analgesia between group B and group C was significant ( $p = 0.001$ ) (Table 2).



**Figure 1: Mean SBP (mmHg) at various time intervals**

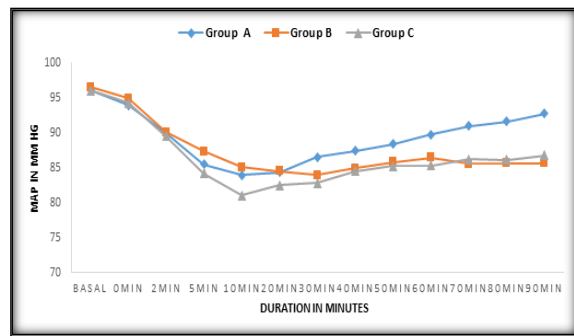
In group A (the control group), the mean SBP at rest is 127.45 mmHg, and we observed a maximal decline of 16.66 mmHg (a 13.08% drop from the mean SBP

at rest) at 10 minutes. In group B (clonidine group), the mean SBP at rest is 128.13 mmHg, and we observed a maximum decrease in mean SBP from mean resting SBP of 17.46 mmHg (13.63% decrease from resting SBP) at the 40th minute. In group C (dexmedetomidine group), the mean SBP at rest is 126.48 mmHg, and we observed a maximal decrease in mean SBP from the mean SBP at rest of 18.66 mmHg at 20th min (14.81% decrease from the mean SBP at rest). Hypotension is defined as a decrease in systolic blood pressure of more than 30% from the baseline or SBP of less than 90 mmHg, so this is not clinically significant. From baseline to the seventieth minute, there is no statistically significant difference in the mean SBP between groups A and B. Between groups A and B, there is a statistically significant difference in the mean SBP from the 70th to 90th minute. The average SBP from rest to 10 minutes does not differ statistically between groups A and C. Between groups A and C, the 20- to 90-minute mean SBP is statistically highly significant. The mean SBP from rest to 90 minutes does not differ statistically between groups B and C.



**Figure 2: Mean DBP (mmHg) at various time intervals**

In group A (the control group), the mean DBP at rest is 81.12mmHg, and we observed a maximal decrease in mean DBP from mean resting DBP of 11.33 mmHg at the 20th minute (a 13.85% decrease from resting DBP). In group B (clonidine group), the mean DBP at rest is 84.651mmHg, and we observed a maximal decrease in mean DBP from mean resting DBP of 16.6 mmHg at 40th min (19.65% reduction from resting DBP). In group C (dexmedetomidine group), the mean DBP at baseline is 81.69.76mmHg, and we observed a maximal decrease in mean DBP from baseline of 13.3mmHg (16.32%) at 10th minute. From baseline to the fifth minute, there is no statistically significant difference in the mean DBP between groups A and B. From the tenth to the ninetieth minute, there is a statistically significant difference in the mean DBP between groups A and B. Between groups A and C, the mean DBP from the second to the tenth minute and from the twentieth to the ninetieth minute is statistically significant. The difference between groups B and C in mean DBP from baseline to 90-minute recordings is not statistically significant.



**Figure 3: Mean MAP (mmHg) at various time intervals**

In group A (control group), the mean basal MAP is 96.47 mmHg, and we observed a maximal drop in mean MAP of 12.2 mmHg from mean basal MAP at 10th min (12.69 % drop from basal MAP). In group B (clonidine group), the basal value of mean MAP is 96.43 mmHg, and we observed a maximal decrease in mean MAP from mean basal MAP of 12.56 mmHg at 30th min (13.01% decrease from basal MAP). In group C (dexmedetomidine group), the basal value of mean MAP is 96.05 mmHg, and we observed a decline in mean MAP which is maximum of 14.96 mmHg from mean basal MAP at 30th min (15.58 % reduction from basal MAP). The mean MAP from baseline to the 60th minute is not statistically different between groups A and B. Between groups A and B, the mean MAP from the 70th to 90th minute is statistically highly significant. The mean MAP from baseline to the 50th minute is not statistically different between groups A and C. The mean MAP from the 60th to 90th minute is statistically significantly different between groups A and C. The mean MAP from baseline to the 90th minute is not statistically different between groups B and group C.

## DISCUSSION

An intrathecal additive to these local anaesthetics is a reliable and reproducible method for prolonging the duration of anaesthesia and also provides postoperative analgesia. In the present study, 90 ASA Grade-I and Grade-II patients scheduled for elective lower limb surgery were randomly divided into three groups (n=30). Asano T et al.<sup>[19]</sup> demonstrated that the binding affinity of dexmedetomidine to spinal alpha-2 receptors is approximately 1:10 that of clonidine. In a study by Kanazi GE et al.<sup>[20]</sup>, the concentrations of dexmedetomidine and clonidine administered were 3g and 30g, respectively. In a study by Sarma et al.<sup>[21]</sup>, the doses of dexmedetomidine and clonidine used were 5g and 50g, respectively. The doses of dexmedetomidine and clonidine were found to be equipotent at a ratio of 1:10 and would induce comparable effects on the characteristics of bupivacaine spinal anaesthesia. Therefore, we utilised 50 g of clonidine and 5 g of dexmedetomidine.

### **Onset of sensory blockage**

In our study, the average duration for the onset of sensory block in the control group is 2.82 minutes, 1.45 minutes in the clonidine group, and 1.17 minutes in the dexmedetomidine group. There is a statistically significant reduction in the onset of sensory blockade in the clonidine and dexmedetomidine groups relative to the placebo group.

In a study conducted by Saxena H et al.<sup>[22]</sup>, the onset of sensory blockade was 6.57 minutes in the control group and 2.58 minutes, 2.54 minutes, and 2.09 minutes in the clonidine group (15 g, 30 g, and 37.5 g, respectively). There was a significant reduction in the onset time, which is consistent with our findings. However, compared to our study, the onset time of sensory block is longer; this may be because the dose of clonidine used was lower than in our study. In a study conducted by Al-Mustafa MM et al.<sup>[23]</sup>, the onset of analgesia was observed to be 9.53 mins in the control group, 6.32 mins and 4.72 mins in the dexmedetomidine group (5 g and 10 g respectively), and in this study there was a significant reduction in the onset time of sensory block, which is comparable to our study. In studies conducted by Dobrydnjov I et al.<sup>[24]</sup>, De Kock M et al.<sup>[25]</sup> in the clonidine group and by Shukla D et al.<sup>[26]</sup> in the dexmedetomidine group, authors observed a significant reduction in the onset time of sensory blockade, which is consistent with our findings.

### **Time taken for utmost sensory blockade**

In comparison to the control group (7.41 minutes), the clonidine (5.91 minutes) and dexmedetomidine group (5.23 minutes) experience a statistically significant decrease in the mean time required for maximal sensory blockade. In a study conducted by Saxena H et al.<sup>[22]</sup> authors observed the mean time to achieve maximum sensory level in control group was 7.31 mins which almost concurs with our study in the control group and 6.82 mins, 7.44 mins and 6.75 mins in clonidine group (15µg, 30µg, 37.5µg respectively) which is more than our study in clonidine group and this may be due to less dose of clonidine used in their study.

Comparable to the study conducted by Shukla D et al.<sup>[26]</sup>, who also observed a significant decrease in the time required for maximum sensory blockade in the dexmedetomidine group, our study demonstrates a significant decrease in the time required for maximum sensory blockade in the dexmedetomidine group.

### **Maximum sensory suppression attained**

In our investigation, T4 level of sensory blockade was observed in 6.7% patients in the control group, 26.6% patients in the clonidine group, and 40.0% patients in the dexmedetomidine group. There is no statistically significant difference between the clonidine and dexmedetomidine groups. In a study conducted by Kanazi GE et al.<sup>[20]</sup>, the peak sensory level attained was T6 in group A (the control group), T6.5 in group B (the clonidine group), and T6 in group C (the dexmedetomidine group), with no significant differences between the groups. In studies

conducted by Al-Ghanem SM et al.<sup>[27]</sup> Gupta R et al.<sup>[28]</sup> and Eid HEA et al.<sup>[29]</sup> with dexmedetomidine and study conducted by Strebel S et al.<sup>[30]</sup> with clonidine, there was no statistically significant difference in the maximum level of sensory blockade. The duration of two segments of sensory block regression

In the present study, regression of sensory block by two segments took 79.49 minutes in the control group, 136.38 minutes in the clonidine group, and 136.35 minutes in the dexmedetomidine group. In comparison to the control group, the clonidine and dexmedetomidine groups experience a statistically significant two-segment increase in the mean time required for sensory block regression. In a study conducted by Kanazi GE et al.<sup>[20]</sup>, authors observed the time required for regression of sensory block by two segments to be 80.28 minutes in the control group, 101.37 minutes in the clonidine group, and 122.37 minutes in the dexmedetomidine group; they also observed a significant prolongation of two segment regression compared to the control group, which is comparable to our findings. Our study is also consistent with the findings of Dobrydnjov I et al.<sup>[24]</sup> Saxena H et al.<sup>[22]</sup> in the clonidine group, and Gupta R et al.<sup>[28]</sup> and Eid HEA et al.<sup>[29]</sup> in the dexmedetomidine group. The authors observed a statistically significant increase of two segments in the mean time required for regression of sensory block.

### **Systolic blood pressure**

In the control group, the maximum drop in mean systolic blood pressure from mean basal systolic blood pressure occurred at 10th minute, whereas in the clonidine and dexmedetomidine groups, it occurred at 40th minute and 20th minute, respectively. None of the differences between the three categories were statistically significant. However, the maximal decrease in systolic blood pressure was slower in the clonidine group compared to the dexmedetomidine group and the placebo group.

### **Diastolic blood pressure**

In the control group, the maximal decrease in mean diastolic blood pressure from mean diastolic blood pressure at rest was 11.33 mmHg at 20 minutes, whereas it was 16.6 mmHg at 40 minutes in the clonidine group and 13.3 mmHg at 10 minutes in the dexmedetomidine group. None of the differences between the three categories were statistically significant. In contrast to the dexmedetomidine group and the placebo group, maximal diastolic blood pressure fell more slowly in the clonidine group than in the dexmedetomidine group and the placebo group.

### **Mean arterial Pressure**

In the control group, the minimum decrease in mean arterial pressure from mean basal MAP at 10 minutes was 12.2 mmHg, in the clonidine group it was 12.56 mmHg, and in the dexmedetomidine group, it was 14.96 mmHg. Regarding MAP decline, there was no statistically significant difference between the three



groups. However, it was discovered that the clonidine and dexmedetomidine groups had a delayed maximum decline in MAP compared to the control group.

In a study conducted by Sethi BS et al.<sup>[31]</sup>, the authors observed the lowest mean arterial pressure (70 mmHg) in the clonidine group (1 g/kg, mean weight 57.93 kg) compared to our study (76.05 mmHg). In a study conducted by Strelbel S. et al.<sup>[30]</sup>, those who received 37.5 g, 75 g, and 150 g of clonidine experienced a maximal decrease in mean arterial pressure of 25%14%, 26%12%, and 25%13%, respectively. In a study by Al-Ghanem SM et al.<sup>[27]</sup>, hypotension (fall in mean arterial pressure of >30% of pre-induction value) was found to be modest to moderate in both the dexmedetomidine and fentanyl groups. 4/38 patients in the dexmedetomidine group and 9/38 patients in the fentanyl group experienced hypotension, but the difference was not statistically significant.

## CONCLUSION

Intrathecal dexmedetomidine supplementation of the spinal block seems to be a good alternative to intrathecal magnesium sulfate, as it produces earlier onset and prolonged duration of sensory and motor block without significant hemodynamic alterations. Dexmedetomidine and clonidine added as adjuvants to intrathecal bupivacaine were found to be effective in elective lower limb surgeries, with respect to block characteristics, hemodynamic changes, and adverse effects.

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