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**ORIGINAL RESEARCH** **BARIATRIC ANESTHESIA**

# Assessing the impact of opioid-free anesthesia using the modified Mulimix technique on postoperative pain in bariatric surgery patients: a correlative randomized double-blinded trial

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## ABSTRACT

**Background & objective:** The effective management of postoperative pain in bariatric surgery poses significant challenges to the anesthesiologists and the surgeons. Opioids have been the mainstay of postoperative pain management; but recently, opioid-free anesthesia (OFA) has been a popular option in an effort to prevent the opioid related side-effects. The objective of this study was to assess the effects of OFA utilizing the modified mulimix technique on the levels of plasma interleukin-2 (IL-2) and interleukin-6 (IL-6). In addition, the study aimed to evaluate the duration of analgesia and the analgesic requirements during the first 24 hours postoperatively.

**Methodology:** A total of 60 patients were randomly assigned to the OFA Group, which received opioid-free anesthesia, and the OBA Group, which received Opioid-Based Anesthesia. The modified Mulimix technique was used in both groups. Serum samples were collected from all patients during skin incision and after the surgical procedure. Subsequently, these samples were assessed for IL-2 and IL-6 levels. The postoperative analgesic consumption was compared in both groups.

**Results:** Regarding serum IL-2 and IL-6 levels in the two study groups, there was a statistically significant difference after the conclusion of surgery, and the skin incision was made. Regarding the initial rescue analgesia postoperatively assessment, the OBA group demonstrated a substantially greater overall consumption of analgesics within the first 24 h. The study revealed a significant difference in VAS values between the OBA Group and the OFA Group at 2 h, 4 h, and 6 h postoperatively.

**Conclusion:** The modified mulimix technique effectively reduces postoperative plasma inflammatory mediators, interleukin-2 and interleukin-6, and results in decreased postoperative pain, thus reducing the postoperative analgesia consumption

**Abbreviations:** OBA - Opioid based anesthesia; OFA - opioid-free anesthesia; IL-2 - interleukin-2; IL-6 - interleukin-6; VAS - visual analogue scale

**Keywords:** Bariatric surgery, interleukin, Mulimix, opioid, pain, immunological response.

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# 1. INTRODUCTION

Many trials have been conducted to overcome the postoperative pain following bariatric surgery. However, each method has its advantages and drawbacks.[1] Utilizing opioid-free anesthesia is a viable technique in bariatric surgery to mitigate various complications, including opioid-induced hyperalgesia, increased risk of obstructive sleep apnea, and postoperative nausea and vomiting.[2] Many controlled trials examining opioid-free anesthesia (OFA) have yielded significant evidence supporting its safety and effectiveness compared to standard opioid-based methods.[3] The immunological response observed during bariatric surgery involves the secretion of specific pro-inflammatory mediators, including interleukin-2 (IL-2) and interleukin-6 (IL-6), which can be influenced by pain and analgesic interventions. IL-6 is a potent biomarker secreted by T-helper cells and macrophages. It induces the release of exocytosis of granules from neutrophils and can regulate the synthesis of prostaglandins. Furthermore, it demonstrates several endocrine functions, including pyrexia induction, body temperature regulation, and hypothalamic-pituitary-adrenal axis activation.[4] In contrast, IL-2 is synthesized by T-helper 1 cells and large granular lymphocytes.[5] In addition, it plays a significant role in initiating numerous cytotoxic and inflammatory responses.[6] Some studies have demonstrated that IL-2 exhibits peripheral antinociceptive or pain-relieving effects. The mechanisms underlying IL-2 antinociceptive efficacy are believed to be mediated through the activation of mu-opioid receptors, which are the same receptors targeted by opioid analgesics such as morphine.[7] Several protocols have been utilized for OFA. However, the "Modified Mulimix" approach, a multimodal mixture developed by Mulier JP involving the administration of loading and maintenance intraoperative doses of dexmedetomidine, ketamine, and lignocaine, has proven to be an effective and versatile method for pain management.[8]

This study aimed to assess the effects of opioid-free anesthesia (OFA) utilizing the modified mulimix technique on the levels of plasma interleukin-2 (IL-2) and interleukin-6 (IL-6) and hence, the duration of analgesia and the analgesic requirements during the first 24 hours postoperatively.

# 2. METHODOLOGY

This prospective, double-blind, controlled, clinical, randomized study was conducted on a sample of 60 patients, both males and females, ages ranging from 20 to 60 y, from October 2022 to December 2023. The study was conducted following the approval of the lOBAl ethics committee No (T.G.H 45/275) by the ethical council of Tadawi General Hospital. All patients provided informed written consent. The research was registered in the ClinicalTrials Registry (No. NCT06216210).

The patients were classified as ASA-II or III, with a BMI ranging from 35-50 kg/m$^2$. The patients were randomized into two equal groups, 30 in each group. The OFA Group was an opioid-free anesthesia group and the OBA Group was an opioid-based anesthesia group.

## 2.1. Study outcomes

The primary outcome was to assess the effects of OFA utilizing the modified mulimix technique on the levels of plasma IL-2 and IL-6. The secondary outcomes were to evaluate the duration of analgesia and the analgesic requirements during the first 24 h postoperatively. We compared the Visual Analog Score (VAS) pain scores between the two groups.

The hemodynamics associated with the two different anesthetic techniques were evaluated to determine the most appropriate approach for bariatric surgery.

## 2.2. Inclusion and exclusion criteria

Patients undergoing bariatric surgery, 20-60 y old, both males and females, ASA-II and III, BMI ranging from 35-50 were included in the study.

Patients who declined participation, pregnant women, patients with communication difficulties that could hinder a reliable postoperative assessment, patients with comorbidities like uncontrolled hypertension, ischemic heart disease, uncontrolled diabetes mellitus, and renal or liver impairment were excluded.

## 2.3. Randomization

Prior to anesthesia starting, all patients were randomly categorized into two groups with computer-generated random numbers that were included inside separate opaque envelopes. The analyzer opened the envelope before starting anesthesia. The blinded anesthetist prepared four syringes; one contained dexmedetomidine for loading, one contained a mixture of dexmedetomidine, ketamine, and lignocaine for the OFA Group, and the third and fourth syringes contained fentanyl for loading and maintenance respectively, for the OBA Group. All syringes were titled with the research drug to retain the double-blinded method of the study.

## 2.4. Anesthetic and surgical procedures

Before surgery, preoperative assessment was done in the form of a detailed history, laboratory tests evaluation, and medical examination. Patients were connected to basal standard monitoring: non-invasive blood pressure, ECG, pulse oximetry, and $EtCO_2$. All basal readings

 

were assessed and documented in the pre-operative preparation area. An intravenous cannula was inserted and a pre-load of normal saline 500 mL was given pre-operatively.

In both groups, patients were administered propofol 2 mg/kg. Cisatracurium 0.15 mg/kg was administered to facilitate tracheal intubation. Intermittent boluses of cisatracurium were administered, and the level of relaxation was assessed based on peripheral nerve stimulation. In both study groups, anesthesia was maintained by administering 2% sevoflurane a mixture of oxygen and air at a flow rate ranging from 3 to 5 L/min. Neuromuscular blockade was continuously monitored via train-of-four monitoring. Atropine and neostigmine were administrated to reverse the effects of the neuromuscular blockade.

The blood samples were collected from the patients and centrifugated at 1600 g for 15 min. Then, the serum was extracted and stored at −80ºC until IL-2 and IL-6 levels were analyzed.

The OFA Group received a multimodal infusion as follows; dexmedetomidine 1 mg/kg intravenously over 10 min before initiation of anesthesia, followed by dexmedetomidine infusion at a rate of 0.5 µg/kg/h throughout the time of surgery. The Modified Mulimix technique, consisting of dexmedetomidine 2.5 µg/mL, ketamine 2.5 mg/mL, and lignocaine 20 mg/mL, was continued throughout the time of surgery at a rate of 20 mL/h. If the patient's weight was 110 kg, the infusion rate was increased by 10 %. The OBA Group (the control group) received opioid-containing anesthesia with fentanyl 2 µg/kg 10 min before the induction of anesthesia, then 0.5 µg/kg/h of fentanyl infusion was started at a rate of 20 mL/h throughout the surgery. Additionally, morphine 0.03 µg/kg was administered at the time of port placement.

Subsequently, the infusion was gradually diminished along with initiating peritoneal insufflation and placing abdominal ports. Following the removal of abdominal ports, the infusion rate was decreased to 5 mL/h, comparable to dexmedetomidine 0.5ug/kg/h. Infusion was temporarily suspended upon completion of the surgical procedure and subsequent closure of the incisions. The administration of a rescue dose of analgesic (specifically, morphine 0.03mg/kg) intravenously after a surgical procedure is recommended when the patient's VAS ≥ 4, either at rest or upon the patient's request.

## 2.5. Measurements

The levels of IL-2 and IL-6 were measured in the serum samples obtained from the patients before induction, after skin incision, at the end of surgery, and 24 hours after the end of surgery using the ELISA technique (Minilyzer, Tecan GmbH, Salzburg, Austria). The commercially available kits (GE Heath Care, Amersham, ELISA Biotrak System, Buckinghamshire, UK) were used following the modified method of Martin et al. (2006).[9]

Mean arterial pressure (MAP) and heart rate (HR) were monitored at regular intervals of 10 minutes until the end of surgery. The pain assessment was conducted after complete patient recovery, as well as at 2, 4, 6, 12, and 24 h postoperatively.

We used the Epi-info TM variant 7.2.4.0 (2020) to calculate the sample size. The reading of two-sided confidence 95%, the test power of 80% and the error state to be 5%. Following the study by Yacout et al.,[10] on pro-inflammatory cytokines, 80 participants were recruited, 20 patients dropped out. Hence, our study comprised 30 patients in each group.

## 2.6. Statistical analysis

We used SPSS software package for social science. Quantitative data were expressed as frequencies and percentages. Results were expressed as mean ± standard deviation (Mean ± SD) for normal distribution data and a median with interquartile range for non-parametric data. The statistical analysis included a Student's t-test to compare the two groups in terms of normally distributed quantitative variables. The Mann-Whitney test was employed to assess the differences between the two groups in terms of non-normally distributed

**Table 1**: **Patients demographic characteristics and duration of surgery**

| Variable | | OBA Group (n = 30) | OFA Group (n = 30) | P-value |
|---|---|---|---|---|
| Age (y) | | 47 ± 8 | 50 ± 7 | 0.127 |
| Weight (kg) | | 119 ± 18 | 113 ± 16 | 0.177 |
| Height (cm) | | 150 ± 14 | 148 ± 12 | 0.554 |
| ASA II / III | | 19/11 | 21/9 | 0.583 |
| Gender | Male | 20 (66.7) | 18 (60) | 0.592 |
| | Female | 10 (33.3) | 12 (40) | |
| Duration of surgery (min) | | 90 ± 23 | 95 ± 28 | 0.452 |
| Duration of anesthesia (min) | | 110 ± 19 | 106 ± 16 | 0.381 |

*Values are expressed as mean ± SD or n (%), Statistically significant (p < 0.05).*

 

quantitative variables. The statistical significance was set at P < 0.05.

# 4. RESULTS

The demographic variables, such as age, sex, weight, and height, as well as the ASA status and duration of operation and anesthesia, were comparable between the two groups under study. No significant differences were observed (P > 0.05) as depicted in Table 1.

Regarding serum IL-2 and IL-6 levels in the two study groups, no statistically significant difference was detected between groups preoperatively and following 24 hours postoperatively (P > 0.05). In contrast, there was a statistically significant difference between the two groups after the conclusion of surgery, and a skin incision was made (P < 0.001), as depicted in Figure 1 and Figure 2.

Regarding the assessment of the initial rescue analgesia postoperatively, a statistically significant difference was observed in the timing of the first morphine dose between the OFA Group and the OBA Group. Furthermore, it is noteworthy that the OBA group demonstrated a substantially greater overall consumption of analgesics within a 24-hour and a greater number of rescue doses administered than the OFA group. This difference was shown to be statistically significant with a p-value of less than 0.001, as shown in Table 2.

The study revealed a significant difference in VAS values between the OBA Group and the OFA Group at 2 hours, 4 hours, and 6 hours postoperatively (P < 0.01). However, no statistically significant difference was observed between the two groups during recovery, specifically at 12 hours and 24 hours after the surgery (P < 0.05), as illustrated in Table 3.

Regarding heart rate (HR) and mean arterial pressure (MAP), no statistically significant distinction was observed between the two study groups (p-value > 0.05), as demonstrated in Figures (3 & 4).

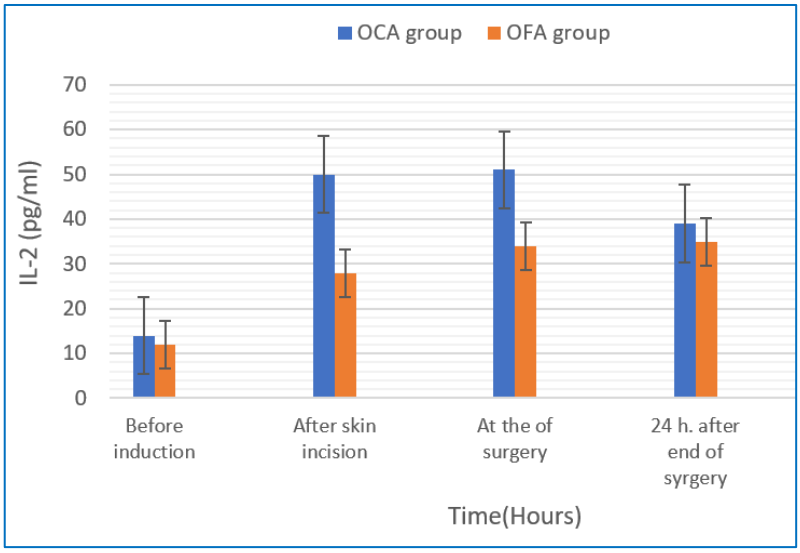


**Figure 1: Interleukin-2 serum level (pg/mL)**

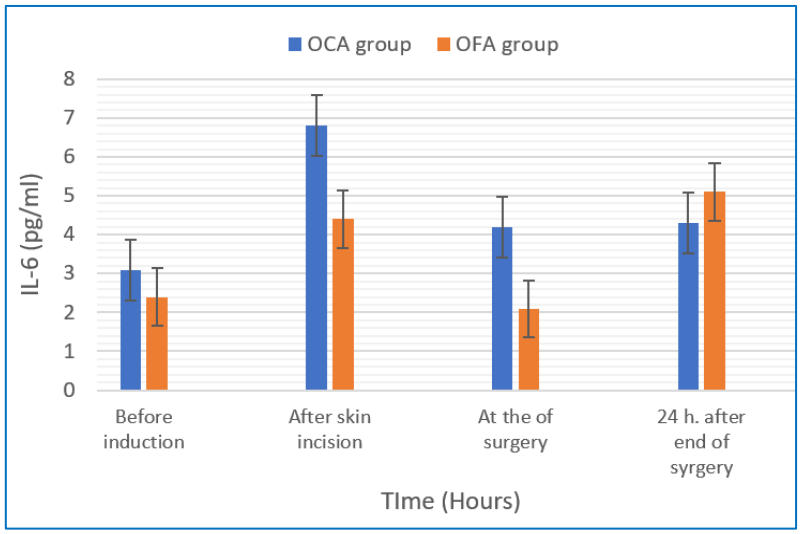


**Figure 2: Interleukin-6 serum level (pg /mL)**

**Table 2: Analgesia duration and analgesic requirements in the 1st 24 hours**

| Variable | OBA Group (n = 30) | OFA Group (n = 30) | P- value |
|---|---|---|---|
| Mean time to first postoperative analgesic requirement (h) | 2.3 ± 1.2 | 4.2 ± 1.5 | < 0.001* |
| Mean total analgesic (morphine) consumption in 24 h (mg) | 15 ± 6 | 5 ± 2.5 | < 0.001* |
| Total number of rescue doses of analgesic | 6 ± 3 | 4 ± 1 | 0.001* |

*Values are expressed as mean ± SD, *: Statistically significant (p < 0.05).*

 

**Table 3: Postoperative VAS scores**

| VAS (IQR-median) | OBA Group (n = 30) | OFA Group (n = 30) | P-value |
|---|---|---|---|
| VAS at recovery | 2 (1-2) | 1 (1-2) | 0.461 |
| VAS 2 h | 3 (2-3) | 2 (1-2) | < 0.01* |
| VAS 4 h | 4 (3-4) | 2 (1-2) | < 0.01* |
| VAS 6 h | 4 (3-4) | 2 (1-2) | < 0.01* |
| VAS 12 h | 4 (3-4) | 3 (3-4) | 0.126 |
| VAS 24 h | 4 (4-5) | 4 (3-4) | 0.161 |

*IQR: interquartile range, VAS: visual analogue scale, *: Statistically significant (p < 0.05).*

# DISCUSSION

The OFA approach is a practice that completely excludes the use of intraoperative systemic, neuraxial, or intracavitary opioids during the anesthetic procedure. It emerged as a viable alternative to conventional opioid-based approaches in the anesthetic management of morbidly obese patients undergoing bariatric surgery.[11]

OFA has the potential advantage of mitigating opioid-related adverse effects in patients. OFA potentially reduces the adverse effects associated with opioids, including respiratory depression, nausea, vomiting, and postoperative drowsiness.[11] Furthermore, OFA provides postoperative pain relief, which aligns with the primary objective of the patient care.

**5.**

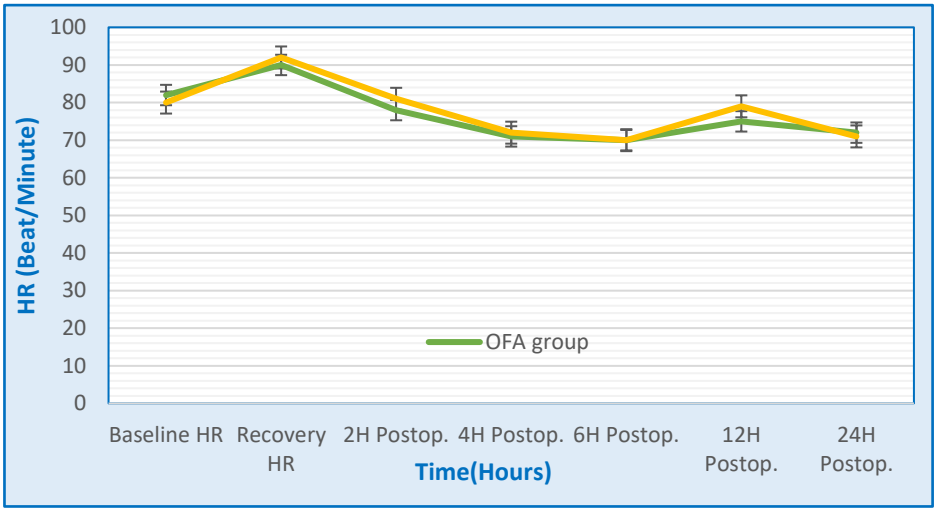


**Figure 3: Heart rate (beat/min); Data presented as mean ± SD**

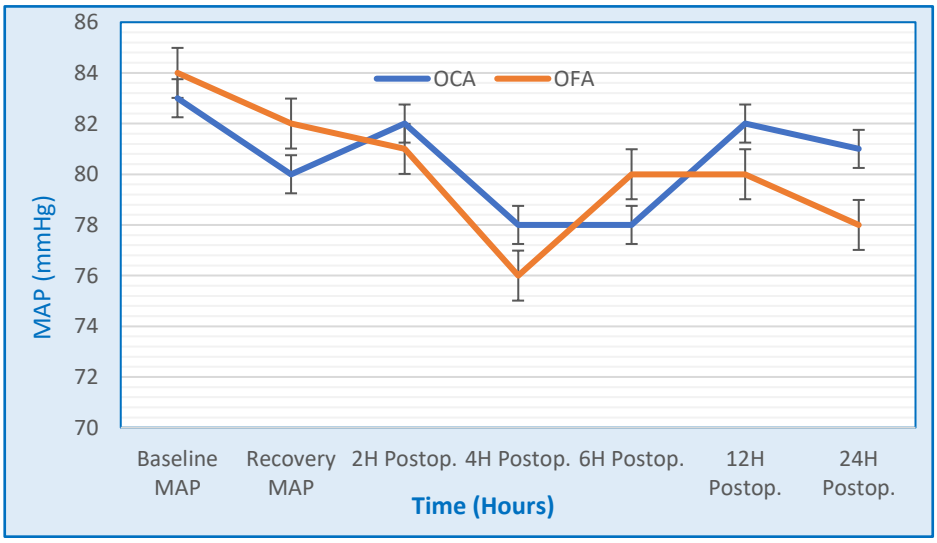


**Figure 4: Mean arterial blood pressure (MAP) mmHg**

 

The current study revealed a significant reduction in plasma levels of IL-2 and IL-6 in the OFA Group compared to the OBA Group, before the skin incision as well as following the conclusion of

the surgery. These findings are consistent with the results reported by Yacout et al. (2012). They evaluated the impact of intravenous dexmedetomidine infusion on stress response markers such as plasma IL-6, cortisol, and blood glucose levels in patients undergoing major abdominal surgery. Their findings revealed that the group treated with dexmedetomidine exhibited significantly lower levels of IL-6, cortisol, and blood glucose compared to the non-treated group.[10] In contrast, Lotfy and Ayaad (2022) demonstrated that serum IL-6 level was significantly elevated 24 h postoperatively in dexmedetomidine-based opioid-free anesthesia techniques, with statistically significant differences. The differences could be due to the subsiding effect of the administered drugs after 24 h, resulting in increased inflammation.[12] This finding aligns with the outcomes of the present study on these cytokines 24 h after surgery. It is noteworthy that elevated IL-2 and IL-6 levels do not necessarily indicate a problem. The immune system is activated, and the release of these cytokines is part of the body's natural response to tissue injury and the healing process.

The results of the current study indicated that the OBA group exhibited higher levels of initial total analgesic consumption within 24 h, as well as a greater number of rescue doses of analgesic, compared to the OFA group. Our results are consistent with the previous study of Sultana et al. (2017) using 'Modified Mulimix' as one of the OFA techniques. The findings revealed a substantial decrease in opioid consumption postoperatively, leading to improved recovery in bariatric surgery, particularly among patients with obstructive sleep apnea.[13]

In the retrospective study conducted by Mulier (2017) that used all consecutive lap Roux-en-Y Gastric Bypass (RNY), patients were divided into three groups: (A) opioid-free Group, (B) opioid anesthesia Group, and (C) opioid-low anesthesia Group. The study findings indicated that patients who underwent OFA demonstrated a shorter hospitalization and required lower or no amounts of opioids on the first day postoperatively.[8] In 2015, Mulier developed a multimodal non-opioid anesthesia technique known as 'Modified Mulimix'. This technique has been found to eliminate the need for opioids during surgery, decrease the dose of opioids needed after surgery, and reduce pain experienced by patients. Our study supports these findings, specifically concerning the total analgesic (morphine) consumption within 24 h and postoperative VAS scores.

Ziemann (2013) conducted a retrospective study involving 181 patients who underwent laparoscopic Roux-en-Y (RNY) gastric bypass surgery. These patients were randomly assigned to two groups: The patient control analgesia (PCA) group was treated with acetaminophen and ketorolac. The Tylenol and Toradol (TNT) group was treated with hydromorphone. The results indicated that patients in the TNT group consumed 1.1 mg of hydromorphone postoperatively, whereas patients in the PCA group consumed 4.2 mg of hydromorphone.[14] So, there was a reduction of 73.8% in opioid consumption in the TNT group. Also, there was a significant reduction in the incidence of postoperative nausea and vomiting in the TNT group ($P < 0.001$). Fortunately, our study did include both ketamine which has beneficial antiemetic effects in addition to its good analgesic effect,[15] and lignocaine which poses a beneficial antiemetic effect also.[16] We did not investigate postoperative nausea and vomiting in this study.

Furthermore, a meta-analysis evaluating the impact of systemic administration of alpha2-agonists on perioperative morphine consumption and postoperative pain intensity demonstrated that alpha 2-agonists exhibit an opioid-sparing effect for up to 24 h postoperatively. This effect resulted in a reduction in the severity of postoperative pain. And reduced the recall for rescue analgesia postoperatively.[9]

# 6. CONCLUSION

The modified Mulimix technique has demonstrated great efficacy in reducing postoperative inflammatory mediators. In addition, it helps in reducing postoperative pain as well as reducing postoperative analgesia consumption.

## 7. Data availability

All data collected during the current study are available with authors.

## 8. Conflict of interests

No conflict of interests declared by the authors. No external or industry funding was involved in this study.

## 9. Acknowledgment

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## 10. Authors' contribution

SHS: Concept, Design, Supervision, Funding -

MME: Materials, Data Collection and/or Processing, Literature Review, Manuscript drafting

AHE: Analysis and/or Interpretation, Critical Review

 

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