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The perioperative analgesic effect of opioid free anesthesia using combination of dexmedetomidine, ketamine and lidocaine in adolescent patients undergoing Scoliosis Surgery; A randomized Controlled Trial

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ABSTRACT

Background: Posterior spinal fusion treatment is one of the most painful options accessible to teenagers with idiopathic scoliosis.

Objectives: This study evaluated the opioid-sparing anesthesia analgesic effect using a combination of dexmedetomidine, ketamine and lidocaine versus opioid-based anesthesia (OBA) with fentanyl in adolescent patients undergoing scoliosis surgery.

Methods: This prospective, double-blinded, randomized study was conducted on 50 patients, American Society of Anesthesiologists (ASA) physical state I–II, scheduled for surgical correction of adolescent idiopathic scoliosis under general anesthesia. Patients were equally categorized into two groups: group I – opioid-free anesthesia (OFA) and group II – OBA. Intraoperative magnesium, total postoperative morphine consumption, time to first postoperative rescue analgesia and adverse effects were recorded.

Results: Total postoperative morphine consumption at 24 h was insignificantly different between groups. The proportion of patients requiring intraoperative magnesium was significantly higher in OBA ($P < 0.001$). Visual analog scale was only significant at 1 and 2 h which was significantly higher in group OBA than group OFA ($P = 0.012$ and < 0.001, respectively). Time to first postoperative rescue analgesia was significantly earlier in OBA than in OFA. Hemodynamic stability was insignificantly different between both groups. Bradycardia, postoperative nausea and vomiting and respiratory depression were insignificantly different between groups.

Conclusions: In adolescent patients ASA I-II undergoing scoliosis correction surgery, OFA with a combination of dexmedetomidine, ketamine and lidocaine could provide adequate intra- and postoperative pain management, which can obviate the use of intraoperative opioids minimizing the total postoperative opioid requirements compared to OBA using fentanyl.

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1. Introduction

Scoliosis surgery is a significant medical surgery in children that often results in considerable postoperative pain. Several analgesics and large opioid dosages are commonly necessary, resulting in a variety of adverse effects. Chronic pain is a frequent complication of surgery [1].

The administration of opioids is regarded as a keystone component in achieving adequate effective analgesia, with hemodynamic stability during anesthesia, although it inhibits the sympathetic system. Unfortunately, opioids used perioperative are associated with sedation, nausea and vomiting, delirium, ileus and respiratory depression, so opioids may not provide optimal postoperative pain control and this may result in chronic pain [2].

In order to gain additive analgesic effects of many medications while limiting their adverse effects, particularly those associated with opioids, opioid-free anesthesia (OFA) multimodal or balanced analgesia is used [3].

OFA includes N-methyl D-aspartate (NMDA) receptor antagonists, e.g. magnesium sulfate and ketamine, sodium channel blocker, e.g. lignocaine, anti-inflammatory drugs, e.g. non-steroidal anti-inflammatory drugs and dexamethasone, sodium channel blockers, e.g. local anesthetics and alpha-2 agonists, e.g. dexmedetomidine and clonidine [4].

Intravenous lidocaine functions as a sodium channel blocker, an NMDA receptor antagonist and an anti-inflammatory. All of these elements contribute to analgesic benefit, a shorter length of stay, a more speedy recovery after surgery and a lower rate of nausea and vomiting [5].

Dexmedetomidine is a selective alpha-2 agonist that has sympatholytic, anxiolytic and analgesic

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characteristics without causing respiratory depression. It decreases opioid usage, pain ratings after surgery and the likelihood of opioid-related adverse events. Dexmedetomidine has been known to produce bradycardia and hypotension in certain patients [6].

Ketamine is an NMDA receptor antagonist. It is an amnesic and provides intense analgesia even at subanesthetic doses. The drug has been successfully employed by continuous infusion, although it has short half-life of 2 to 3 h [7].

Magnesium sulfate is NMDA receptor antagonists important in modulation and sensitization of central nociceptive pathways and enhances the analgesic properties of other analgesics when used as an adjuvant agent [8].

We hypothesized that a combination of dexmedetomidine, ketamine and lidocaine would provide effective intraoperative and postoperative analgesia for patients undergoing adolescent scoliosis correction surgery, thereby reducing the use of opioids and the risk of adverse effects in this high-risk patient population.

The aim of this study was to evaluate the analgesic effect (intraoperative magnesium, total postoperative morphine consumption and time to first postoperative rescue analgesia) of opioid-sparing anesthesia using a combination of dexmedetomidine, ketamine and lidocaine versus opioid-based anesthesia (OBA) with fentanyl in adolescent patients undergoing scoliosis surgery.

2. Patients and methods

This prospective, double-blinded, randomized study was conducted at Tanta University Hospitals over a period of 1 year from November 2020 to November 2021 after approval from the institutional ethical committee with clinical trial registry number (PACTR202011865064201). An informed written consent was obtained from patients' parents or their guardians with an explanation of the procedure's benefits and risks before participation in the study.

Fifty patients of both sexes aged 10 to 18 years, American Society of Anesthesiologists (ASA) physical state class I–II, were scheduled for surgical correction of adolescent idiopathic scoliosis under general anesthesia (GA).

The patients' guardian refusal, preexisting neurological or psychiatric illnesses, mental retardation, hepatic or renal insufficiency or hematological disorder, contraindication or allergy to study medications, unstable cardiorespiratory disorder or any degree of heart block, chronic use of opioids, and non-idiopathic scoliosis were the exclusion criteria.

3. Randomization

Using a computer-generated random number system concealed in sealed opaque envelopes, and patients were divided into two groups (25 patients in each group): group I OFA and group II OBA.

One anesthetist performed GA using either OFA or OBA, while another gathered data (without being informed by the group assignment). All drugs were prepared in identical syringes that cannot be distinguished from each other and coded with numbers. Nurses and patients in PACU were blinded to the group assignment.

Preoperative assessment was done by history taking, clinical examination and investigation. The whole procedure was explained to patients and guardians, and at that time, patients were trained how to use 10 cm visual analogue scale (VAS): with 0 as no pain and 10 as the worse possible pain one can imagine.

On arrival to the operating room, standard monitoring (Cardio caps/5; Datex-Ohmeda, Helsinki, Finland) was applied to all patients including heart rate (HR), mean arterial pressure (MAP), arterial oxygen saturation (SpO_2), electrocardiogram and pulse oximetry.

All patients received 0.03 mg/kg midazolam prior to GA induction. Preoxygenation with 100% O_2 was performed for 3 min before induction of anesthesia.

For all patients, induction of GA was done by IV administration of propofol (loading 1.5 to 2.5 mg/kg then 50–200 µg/kg/min maintenance) and atracurium (0. 5 mg/kg atracurium then increments 0.1 to 0.2 mg/kg).

Patients in opioid-based group received fentanyl (loading 1 mic/kg then continuous intraoperative infusion 0.5 µg/kg/h) and two syringes with normal saline 0.9% which infused at the same rate, while patients in opioid-free group received dexmedetomidine (loading 1 µg/kg, continuous intraoperative infusion 0.3–0.5 µg/kg/h), lidocaine (loading 1.5 mg/kg, infusion 2 mg/kg/h) and ketamine infusion 0.1–0.3 mg/kg/h started after the induction of anesthesia and before the skin incision. All loading doses of the drugs were injected in 10 min before the induction of GA. Infusion rate of the drugs was changed to maintain bispectral index (BIS) between 40 and 60 [3,9,10].

After intubation, electrodes of entropy for monitoring the depth of anesthesia were attached, and left radial artery cannulation was done. Maintenance of anesthesia patient was by oxygen–air mixture: 50:50%, and patients were mechanically ventilated with ventilator settings adjusted to maintain end tidal CO_2 between 35 and 40 mmHg.

For both groups, boluses of magnesium sulphate 50 mg/kg were given as a rescue co-analgesic in case of presence of hypertension (MAP) >20% from baseline) or tachycardia while maintaining BIS between 40 and 60.

Both groups received dexamethasone (8 mg i.v.) and ondansetron (4 mg i.v.) 15 min after induction of GA and 20 min prior the surgery was completed [3].

To reverse the neuromuscular blockade, neostigmine (0.05 mg/kg) and atropine (0.01 mg/kg) were given intravenously after surgery. Extubation was performed when the patient's tidal volume surpassed 4 ml/kg. Throughout the surgery, the respiratory rate, MAP, HR and oxygen saturation were measured.

Postoperative analgesia IV acetaminophen 15 mg/kg (maximum 1000 mg) was given every 6 h, with first dose given intraoperatively before extubation [11]. Postoperative rescue analgesia was intravenous morphine in a dose of 0.1 mg/kg. It was given if VAS score was more than 4 or upon request of the patients.

4. The following measurements were evaluated

Primary outcome [number of patients needed intraoperative magnesium] and secondary outcomes [time of first postoperative analgesic requirement, total postoperative morphine consumption at 24 h and pain score assessed by 10 cm visual analog scale (VAS) at the following times: on arrival to PACU, then 1, 2, 4, 6, 12, 18 and 24 h postoperative] were evaluated. Side effects [postoperative nausea and vomiting (PONV), hypotension (MAP <20% of baseline was overcome by ephedrine 5 mg IV and/or normal saline IV), bradycardia (HR <60 beats/min and was controlled by atropine 0.6 mg IV) and respiratory depression] were recorded.

5. Sample size justification

The sample size was calculated as regard our primary outcome variable which was the proportion of patients requiring intraoperative rescue analgesia. Based on the results of a previous study [12], the percentage of patients requiring intraoperative rescue analgesia in the OBA group was 70.9%. Hence, a sample size of 22 participants was needed to identify a 50% difference in the number of patients needing intraoperative rescue analgesia between the opioid-free and opioid-containing groups with a 0.05 error and 95% power. As a result, we included 25 patients in each group to account for possible dropouts.

6. Statistical analysis

The SPSS 16.0 computer statistical software system was used to analyze the data (SPSS Inc., Chicago, IL, USA). To check the assumption of normality, the Shapiro–Wilk test was used. Student's t-test or Mann–Whitney U-test was used to compare the continuous data, which was presented as mean ± standard deviation (SD) or median with interquartile range. Fisher's exact test or chi-square test was used to compare categorical data, which was expressed in the form of number (*n*) and/or percentage (%). The level of significance was adapted at *P* value <0.05.

7. Results

In our trial, 63 patients were eligible for assessment, nine cases did not meet the criteria, and four patients did not agree to participate in the study. We enrolled 50 cases randomly divided into two groups (25 cases in each), OFA and OBA groups. No cases were lost during the follow-up or discontinued the intervention. So, 50 cases were analyzed [Figure 1].

Patient's demographics data (age, gender, weight, ASA physical state class and duration of surgery) were insignificantly different between both groups [Table 1].

There were 3 (12.0%) patients who required intraoperative magnesium in group OFA and 13 (52.0%) patients in group OBA. Patients required intraoperative magnesium was significantly higher in group OBA than group OFA ($P = 0.005$). Time of first postoperative analgesic requirement had a mean value of 4.4 ± 1.63 h in group OFA and 2.5 ± 1.19 h in group OBA. Time of first postoperative analgesic requirement was significantly longer in group OFA than group OBA ($P < 0.001$). Total postoperative morphine consumption at 24 h had a mean value of 13.9 ± 5.43 mg in group OFA and 13.0 ± 4.99 mg in group OBA. Total postoperative morphine consumption at 24 h was insignificantly different in group OFA than group OBA [Table 2].

VAS was insignificantly different at all time measurements except at 1 and 2 h postoperatively which was significantly higher in group OBA than group OFA ($P = 0.012$ and <0.001, respectively) [Table 3].

Bradycardia occurred in four (16.0%) patients in group OFA and one (4.0%) patient in group OBA. PONV occurred in two (8.0%) patients in group OFA and six (24.0%) patients in group OBA. Respiratory depression did not occur in group OFA and in one (4.0%) patient in group OBA. All side effects (bradycardia, PONV and respiratory depression) were insignificantly different between both groups [Table 4].

8. Discussion

According to the main findings in our study, the OFA group provided more adequate analgesic effect through a significant reduction in intraoperative magnesium requirement and longer time of first postoperative analgesic requirement compared to OBA group. Total postoperative morphine consumption at 24 h was insignificantly different between the groups. VAS was significantly higher in group OBA than group OFA only at 1 and 2 h postoperatively with insignificant difference in the incidence of the adverse effect between the two groups.

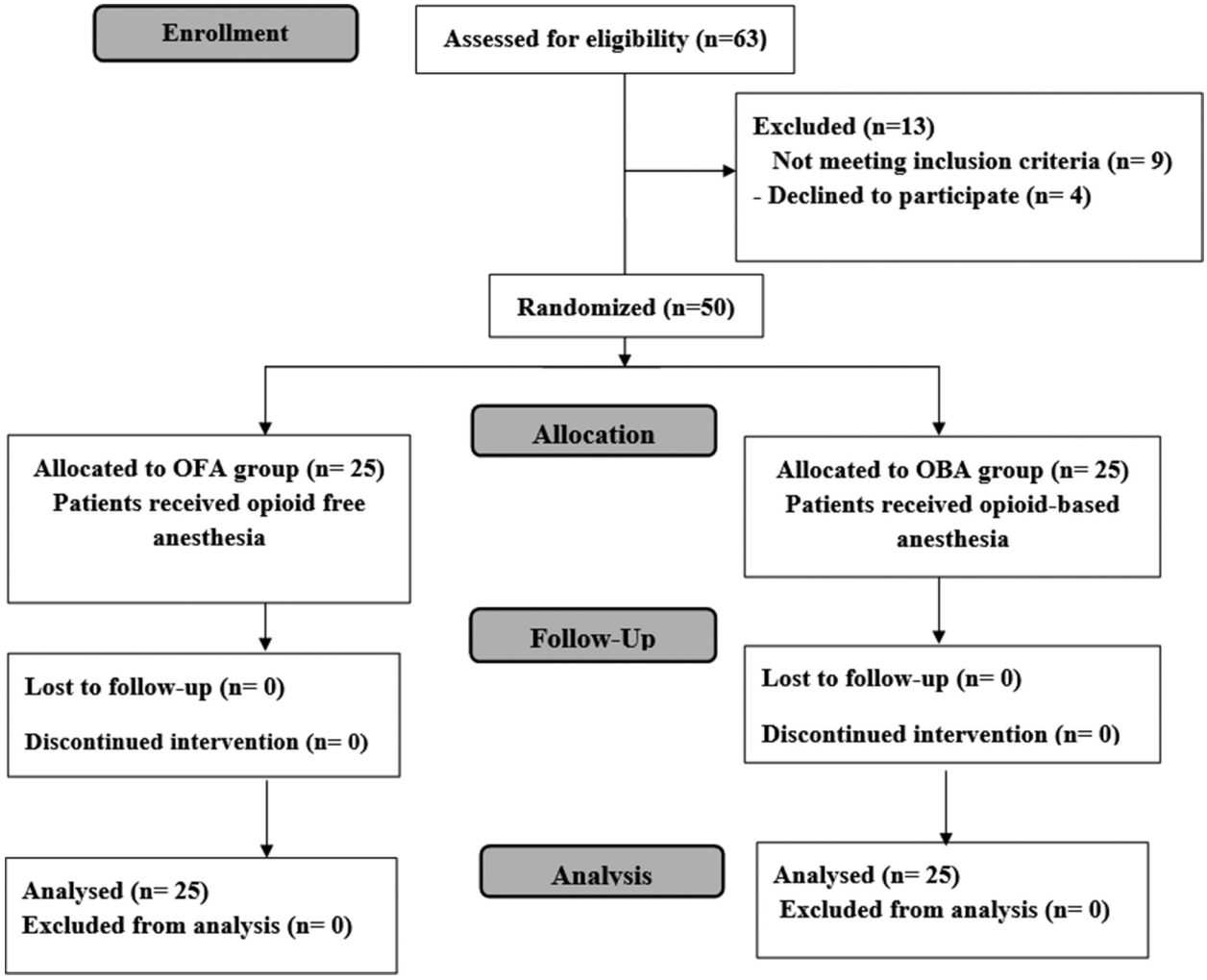

Figure 1. The CONSORT flow diagram, including enrollment, intervention allocation and analysis.

Table 1. Demographic data and patients characteristic in the two studied groups.

		OFA group ($N = 25$)	OBA group ($N = 25$)
Age (years)		15 ± 2.35	14 ± 2.55
Gender	Male	14 (56.0%)	12 (48.0%)
	Female	11 (44.0%)	13 (52.0%)
Weight (kg)		58.0 ± 9.52	56.0 ± 1.23
ASA physical status	I	12 (48.0%)	15 (60.0%)
	II	13 (52.0%)	10 (4.0%)
Duration of surgery (min)		200 ± 35.65	204 ± 32.273

Note: Data are presented as mean ± SD or frequency (%). ASA: American Society of Anesthesiologists, OFA: opioid-free anesthesia, OBA: opioid-based anesthesia. There were no statistically significant differences between the two groups. P-value <0.05 is considered statistically significant.

Several analgesic techniques are available for the management of pain associated with this procedure; however, no one modality has been shown to be superior. Traditionally, intravenous opioids have been used for patient-controlled analgesia in many centers, but these drugs have a variety of undesired side effects, such as nausea and vomiting, delirium, ileus and respiratory depression when administered intrathecally. In addition to epidural analgesia, a high rate of failure may interfere with postoperative neurologic evaluations. Urinary retention, respiratory depression and itching are all possible side effects of intrathecal morphine [13].

Recent studies indicate that OFA induces multimodal pain management with improved analgesia quality and reduces adverse effects associated to opioid use (nausea, vomiting, constipation, pruritus, dizziness, dry mouth and sedation) [14].

Opioids might be avoided during surgery and substituted with analgesic drugs to help manage the effects of surgical trauma under anesthesia; however, this suggestion requires additional research [15].

Table 2. Patients required intraoperative magnesium, time of first postoperative analgesic requirement and total postoperative morphine consumption at 24 h in the two studied groups.

	OFA group ($N = 25$)	OBA group ($N = 25$)	P value
Patients required intraoperative magnesium	3 (12.0%)	13 (52.0%)	0.005*
Time of first postoperative analgesic requirement (h)	4 ± 1.63	3 ± 1.19	<0.001*
Total postoperative morphine consumption at 24 h (mg)	14 ± 5.43	13 ± 4.99	0.543

Note: OFA: opioid-free anesthesia, OBA: opioid-based anesthesia. * P value <0.05 is considered statistically significant.

Table 3. Visual analog scale in the two studied groups.

	OFA group ($N = 25$)	OBA group ($N = 25$)
PACU	2 (1–3)	2 (1–2)
1 h postoperatively	2 (1–2)	3 (2–3)*
2 h postoperatively	2 (1–2)	3 (3–5)*
4 h postoperatively	3 (2–4)	2 (2–5)
6 h postoperatively	3 (1–4)	2 (2–3)
12 h postoperatively	3 (2–5)	3 (2–4)
18 h postoperatively	3 (2–5)	4 (2–5)
24 h postoperatively	4 (2–5)	2 (1–5)

Note: Data are expressed as median (IQR: Interquartile range). OFA: opioid-free anesthesia, OBA: opioid-based anesthesia, PACU: post-anesthesia care unit, *P-value <0.05 compared to OFA group.

Table 4. Side effects in the two studied groups.

	OFA group ($N = 25$)	OBA group ($N = 25$)
Bradycardia	4 (16.0%)	1 (4.0%)
PONV	2 (8.0%)	6 (24.0%)
Respiratory depression	0 (.0%)	1 (4.0%)

Note: Data are expressed as number and frequency (percentage). OFA: opioid-free anesthesia, OBA: opioid-based anesthesia. PONV: postoperative nausea and vomiting. There were no statistically significant differences between the two groups. P-value <0.05 is considered statistically significant.

Hence, our study represented a trial to evaluate this suggestion using OFA regimen including dexmedetomidine, ketamine and lidocaine in scoliosis surgery.

In this regard, Ahmed et al. [12] presented a study on 62 patients scheduled for laparoscopic cholecystectomy. The OBA group received fentanyl as the primary anesthetic adjuvant and peri-operative analgesic, while the OFA group received dexmedetomidine, ketamine and paracetamol. The study revealed that the OBA group required more intraoperative analgesia than the OFA group.

Moreover, Mendonça et al. [16] showed that the patients who received both lidocaine and magnesium sulfate group consumed less intraoperative rescue analgesia in the form of alfentanil during surgery.

Additionally, Bhardwaj et al. [3] enrolled 80 patients aged 20–60 years undergoing laparoscopic urological procedures under GA. Patients in the opioid-free group required much less rescue analgesia. In addition, the opioid-based group needed the first dose of rescue analgesic substantially earlier than the opioid-free group did. Opioid-based groups required considerably more total analgesic dosage than opioid-free groups. These results may be contributed to that the ketamine–lidocaine combination produces central desensitization of the pain pathways and an anti-inflammatory and anti-hyperalgesic effect in a synergistic manner [17].

Moreover, Hassan et al. [18] added Mg to ketamine infusion in cancer breast surgery which can safely improve intraoperative and postoperative analgesia with opioid-sparing effect as it reduced intraoperative fentanyl consumption.

We are also in accordance with similar results that were obtained by Boysen et al. [7] who used lidocaine and dexmedetomidine infusion in stent placement for chronic pancreatitis. Postoperative, patient received acetaminophen 1 g/6 h intravenous and pain relieved without opioids.

Furthermore, Ibrahim et al. [19] performed ultrasonic-guided thoracic epidural with pre-induction by precedex, ketamine, xylocaine, esmolol, dexamethasone, paracetamol and magnesium. There was significant decrease in pain scores within 24-h postoperative p-value <0.05, and there was a clinically significant reduction in time for outcome from the recovery room for OFA group.

Similarly, in a case report, lumbosacral posterior spinal fusion [6] used dexmedetomidine and lidocaine (without intraoperative opioids) for a 65-year-old man undergoing spine surgery. Postoperative, the numeric rating scale of pain was 3/10.

In addition, the data obtained by Mulier et al. [20] were in accordance with our results. They found that OFA provided lower opioid consumption with higher quality of recovery than OBA in patients undergoing laparoscopic bariatric surgery.

As regards PONV, respiratory depression and intraoperative bradycardia, there was no statistically significant difference between both studied groups although there was a decrease in PONV incidence in OFA. Respiratory depression did not occur in group OFA and in one (4.0%) patient in group OBA. Only four cases of bradycardia were reported in OFA group (managed by atropine 1 mg) as it reduces the intraoperative opioid administration and provides better hear rate controlling. Similar to our results, studies by Ahmed et al. [12] and Kim et al. [6] demonstrated that there were reduction of adverse effects e.g., PONV and respiratory depression in OFA.

Supporting our results, a recent randomized study showed that OFA with dexmedetomidine, ketamine and sevoflurane did not reduce PONV or pain after gynecological laparoscopic surgery [21]. In contrary, Ziemann-Gimmel et al. [22] reported that OFA strategy with ketamine, dexmedetomidine and propofol reduced the incidence and severity of PONV after bariatric surgery.

In contrast to our results, Ahmed et al. [12] demonstrated that in both OA and OFA there was no statistically significant difference regarding analgesic consumption, VAS score postoperatively and discharge, but this may be due to different type and duration of surgery (lap cholecystectomy); in addition, they did not use lidocaine.

There are some limitations. It was a single-center study, so the results cannot be generalized. The sample size was relatively small, and the results may differ elsewhere. Moreover, the study used dexmedetomidine that contributes to complications including hypotension and bradycardia which must be considered when administered. Therefore, further trials are needed to use different doses of dexmedetomidine

to know the optimum and safe lowest dose. Additional constraints include the best method for monitoring intraoperative pain, the best non-opioid medication to utilize as intraoperative rescue analgesia and which anesthetic and analgesic adjuvants to include in the regimen.

9. Conclusions

In adolescent patients ASA I-II undergoing scoliosis correction surgery, OFA with combination of dexmedetomidine, ketamine and lidocaine could provide adequate intra- and postoperative pain management, which can obviate the use of intraoperative opioids, minimizing the total postoperative opioid requirements compared to OBA using fentanyl.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Availability of data and material

The datasets used and/or analyzed during the current study are available as MS Excel files (.xlsx) from the corresponding author upon reasonable request.

Ethical approval and protocol registration

This prospective, double-blinded, randomized study was conducted at Tanta University Hospitals over a period of 1 year from November 2020 to November 2021 after approval from the institutional ethical committee with clinical trial registry number (PACTR202011865064201). An informed written consent was obtained from all patients with an explanation of the procedure's benefits and risks before participation in the study.

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