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Subtenon versus intravenous Dexmedetomidine injection for postoperative analgesia in infantile cataract surgery: double-blind randomized clinical trial

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ABSTRACT

Background: Subtenon block (SB) is one of the optimal opioid-free modalities for pain alleviation in cataract extraction surgery. Dexmedetomidine can be used as an adjuvant to local anesthetic regional blocks offering better analgesia. Our primary novel goal is to study the effect of dexmedetomidine-bupivacaine SB versus intravenous dexmedetomidine upon the number of infants who require postoperative analgesia after congenital cataract extraction. **Methods**: 80 infants undergoing cataract extraction were randomly allocated into two groups. **SB group (n = 40)** SB block done with a mixture of 0.05 ml/kg of 0.5% bupivacaine and 0.5 ug/kg dexmedetomidine, and **IV group** (n = 40) received 1 ug/kg dexmedetomidine intravenously after anesthesia inductions included the number of infants required rescue analgesia and CRIES pain score during the 1st four hours postoperatively. **Results**: The incidence of rescue analgesia need was significantly lower in the SB group 2 infants versus 11 in SB and IV groups in consequence (p = 0.006). CRIES score was of significantly lower values in SB group than IV group post-arousal at 20th and 40th min., and 1st,2nd, and 3rd hours (p-values; 0.01, 0.019, <0.001, <0.001, 0.001 in consequence). Limitation: No control group was included. Limitations: Lack of control group and short follow-up period. **Conclusion**: Subtenon block with a mixture of 0.5 ml kg of 0.5% bupivacaine and 0.5 ug/Kg dexmedetomidine offers advantages of being safe and more effective for postoperative analgesia over intravenous dexmedetomidine in infants undergoing cataract extraction surgery during the early postoperative period.

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Postoperative pain; cries score; dexmedetomidine; subtenon block; congenital cataract; pediatric anesthesia

1. Introduction

The optimal time to extract congenital cataract in infants has been evidenced to be at the age of 4–6 weeks [1]. Operative intervention in such a group of patients is always done under general anesthesia. Opioid analgesia in this age category offers optimal postoperative pain relief; however, respiratory depression and frequent emesis are a major concern [2]. Subtenon block (SB) is an attractive opioid-free regional anesthesia adjunct to general anesthesia in infants and children. Subtenon block can reduce the anesthetic requirements and offer good perioperative analgesia [3].

Dexmedetomidine (DEX) is an alpha-2 adrenergic receptor agonist. It carries sedative and analgesic properties (without depressant effects upon respiratory rate) and is now also commonly used as an adjuvant in general anesthesia, nerve block, and postoperative analgesia [4]. The use of local DEX infiltration for pain relief is well established; it can be used as an adjuvant to local anesthetic in eye surgery [5].

Post-operative pain and crying without emesis should be avoided especially in intraocular surgeries. We have built our novel hypothesis regarding the use of local DEX along with bupivacaine in SB block versus IV DEX for optimal pain. **The primary outcome** of our study was the number of infants requiring rescue analgesia in each group. **Secondary outcomes** were overall pain CRIES score [6], vomiting score, and intervention-related complications.

2. Materials and methods

This is a prospective randomized controlled double-blind study and was conducted in Assiut university hospital. Approval from the local institutional ethics committee was firstly obtained; the study then was registered on clinical trials.gov under the number of (NCT02495220). As a role, we enrolled and treated the patients with complete adherence to the last Declaration of Helsinki [7]. Written informed consent was obtained from parents or legal guardians.

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We included 80 ASA physical status I and II infants (aged 1 to 12 months) undergoing elective cataract extraction surgery in one eye. Infants with any orbital infection increased intraocular pressure, history of allergy to local anesthetics, previous eye surgery, cardiovascular, inner ear, or clotting disorders, a full stomach, or other conditions which predispose vomiting, airway abnormalities, or compromised sclera were excluded from the study. Before the procedure, the patients fasted for six hours without food, and for three hours without fluid. Participants received no premedication. Randomization was established by the aid of computer-generated random numbers, and the patients were equally enrolled into two groups.

Group (SB) (n = 40) infants received subtenon blocks after anesthesia induction, and the block was done by a mixture of 0.05 ml/kg of 0.5% bupivacaine and 0.5 ug/kg dexmedetomidine (maximum volume 2 ml) administrated by the surgeon. **Subtenon block technique**: topical proxymetacaine 0.5% was applied, and a small inferonasal conjunctival and tenon capsule incision was made to gain access to the sub-tenon space. After the bare sclera was seen, a curved metallic cannula was passed through the limbal aperture beyond the equator of the globe and DEX-bupivacaine mixture was delivered into the subtenon space [3].

Group (IV) (n = 40) infants received 1 ug/kg DEX iv infusion after anesthesia induction over 10 minutes.

Upon the arrival of patients into the operating room, anesthesia was induced with an 8% concentration of sevoflurane in 100% oxygen using a face mask with infant T-piece anesthesia circuit under the monitoring of ECG, pulse oximetry (Spo2), and noninvasive blood pressure (NIBP). A 22-G cannula was inserted and normal saline of 3 ml/kg/h was infused after induction of anesthesia. After insertion of the laryngeal mask airway (size 2–2.5), sevoflurane concentration (1–2%) in 100% oxygen (SPO2 goal >95%). Respiratory parameters were monitored (goals; End-tidal CO2 partial pressure (ETCO2) of 40–45 mm Hg, tidal volume of 7.0–10 ml/kg, and a respiratory rate of 20–25 breath/min). Ventilation was assisted in case of apnea/hypopnea or if the infant's ETCO2 > 50 mmHg. Interventions were done just after induction, and surgery was started 5 minutes after study drug administration. At the end of the surgery, sevoflurane inhalation was stopped the laryngeal mask airway was removed. Intraoperatively, oculocardiac reflex (OCR) was defined as a sudden decrease in heart rate by more than 20%, or any arrhythmia during surgery. Fentanyl 0.5 ug/kg was administrated if the patient's heart rate or blood pressure increased by ≥20% during surgery, and the infant was excluded from the study.

Respiratory rate, oxygen saturation, end-tidal carbon dioxide, heart rate (HR), and mean arterial blood pressure (MAP) were recorded as baseline values, after induction, 5 minutes after the intervention, then at 5-min intervals until the end of surgery. Complications related to the block or chemosis leading to any surgical discomfort were also noted.

Parents and postoperative assessment physician were kept blinded to patient group assignment. As a primary goal, the number of infants who requires rescue analgesia (when CRIES>6) is recorded. Postoperative CRIES pain score was recorded at 0 min (immediately after shifting to the postoperative care unit) 20^{th} and 40^{th} min., then after the 1^{st}, 2^{nd}, 3^{rd}, and 4^{th} hours postoperatively. Rescue analgesia was in the form of 7.5 mg/Kg of intravenous paracetamol.

The number of episodes of vomiting (defined as the forceful oral expulsion of liquid or solid gastric contents or retching considered as vomiting events) was recorded throughout the 4 hours postoperatively using a numeric rank score (0 = no vomiting, 1 = vomited once, and 2 = vomited twice or more) [8]. Infants experiencing more than two emetic episodes were treated with ondansetron 100 ugm/kg that can be repeated up to a total dose of 4 mg. Complications related to the procedure were recorded.

3. Statistical methods

The sample size was calculated and based upon the previous study done by Sethi et al. [3] where they compared SB versus IV fentanyl mainly for the number of children who require rescue analgesia, they have included 32 children per group, we have enrolled 40 children to compensate for any dropout. Data are presented mean± standard deviation or standard error, ratio, number (percentage), and/or median with an interquartile range as appropriate. Numerical data were firstly tested for normality through Kolmogorov–Smirnov Z-test. The incidences were analyzed by the chi-square test or Fisher's exact test. Categorial data were analyzed by the chi-square test. The comparisons between groups regarding continuous data were attained through Mann–Whitney U-test and unpaired t-test for nonparametric and parametric variables in consequence. $P < 0.05$ was considered statistically significant. Statistical analysis was established using the computer software IBM, SPSS (Statistical Package for Social Sciences), Version 22, 2015.

4. Results

The patients were comparable regarding demographic data and anesthesia/surgical times with no insignificant difference between the two groups (Table 1). The 80 participants completed the study as shown in the CONSORT flow chart (Figure 1).

The number of infants who required rescue analgesia was significantly lower in the SB group than the IV

Table 1. Demographic and clinical data of the studied groups.

Variables	Subtenon group (SB)(n = 40)	Intravenous group (IV)(n = 40)	*P*-value
Age (months)	7.2 ± 1.93	6.9 ± 1.92	0.57
Weight (Kg)	7.79 ± 0.76	7.57 ± 0.72	0.19
Height (cm)	64.42 ± 11.5	66.2 ± 4.1	0.36
Male/Female	22/18	21/19	1
Surgery duration (minutes)Anesthesia duration	31.75 ± 2.641.35 ± 2.32	31.9 ± 2.542.38 ± 2.19	0.060.052
Complications	1 (2.5%)2 (5%)	3 (7.5%)3 (7.5%)	0.621
• Arrhythmia			
• Oculo-cardiac reflex			
Number of infants requiredrescue analgesia	2/38(5%)	11/29(27.5%)	0.006
Vomiting	2(5%)1(2.5%)1 (2.5%)	2(5%)1(2.5)1 (2.5%)	111
• Score 1			
• Score 2			
• Rescue anti-emetic			

Data are presented mean± standard deviation (SD), ratio, or number (percentage). $P < 0.05$ is considered statistically significant.

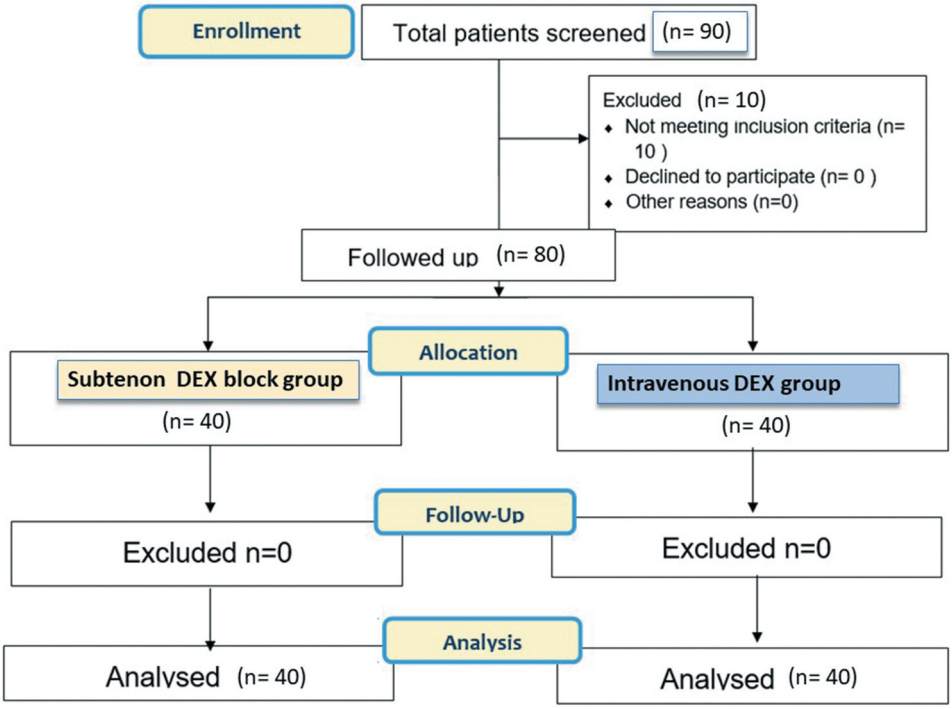

Figure 1. CONSORT- Flow chart of the participants.

group with *p*-value = 0.006 (Table 1). CRIES score was significant of lower values in the SB injection group starting from 20 minutes after arousal until the 3rd postoperative hour of follow-up period as shown in Table 2.

The incidence of vomiting and the need for antiemetics showed a non-significant difference between the two groups. Arrhythmia and oculocardiac reflex have occurred in both groups with an insignificant difference in between (Table 1)

Intraoperative respiratory rate was significantly higher in the intravenous group after induction and continued to be high until the 20th minute (Table 3). ETCO2 was significantly lower in the intravenous group after induction, then became significantly higher after 10 minutes of induction. SPO2 was significantly higher in the intravenous

Table 2. CRIES score changes of the studied groups.

Variables	Subtenon group (SB) (n = 40)	Intravenous group (IV) (n = 40)	*P*-value
0-minute	1.7 ± 0.112(1)	1.85 ± 0.122(1)	0.34
20 minutes	1.28 ± 0.121(1)	1.78 ± 0.112(1)	0.01
40 minutes	1 ± 0.11(2)	1.4 ± 0.11(1)	0.019
1 hour	0.55 ± 0.10(1)	1.25 ± 0.11(1)	<0.001
2 hours	0.4 ± 0.080(1)	0.95 ± 0.11(1)	<0.001
3 hours	0.13 ± 0.050(0)	0.48 ± 0.080(1)	0.001
4 hours	0.05 ± 0.030(0)	0.18 ± 0.060(0)	0.079

Data are, mean± standard error (SE) or median (interquartile range). $P < 0.05$ is considered statistically significant.

Table 3. Intraoperative respiratory rate (Breath/minute) changes of the studied groups.

Variables	Subtenon group (SB)(n = 40)	Intravenous group (IV)(n = 40)	*P*-value
Baseline	29.6 ± 2.5	30.8 ± 2.3	0.036
After induction	27.4 ± 2.6	29.6 ± 2.3	<0.001
5 minutes	26 ± 1.9	28 ± 2	<0.001
10 minutes	25.4 ± 1.4	27.3 ± 1.7	<0.001
15 minutes	25 ± 1	26 ± 1	<0.001
20 minutes	25 ± 1	25.8 ± 1	0.033
25 minutes	24.9 ± 1	25 ± 1	0.16
30 minutes	24.5 ± 0.8	24.8 ± 1	0.24

Data are, mean± standard deviation (SD). $P < 0.05$ is considered statistically significant.

group after the 5th and 10th minutes of induction (Table 4).

Intraoperative hemodynamics: HR was significantly higher in the intravenous group at 15th,20th, 25th, and 30th minutes (Figure 2). Regarding MAP, it was significantly higher in the intravenous group just after induction and at the 5th and 10th minutes as shown in Figure 3.

No mishaps or complications related to the maneuver have occurred.

5. Discussion

In this study, we evaluated analgesia requirements and pain scores in infants undergoing cataract surgery. We noted that SB dexmedetomidine is safe and more effective regarding perioperative analgesia compared to IV dexmedetomidine for in infants undergoing cataract surgery under general anesthesia. Fewer infants required rescue analgesia and consequently lower CRIES pain scores were observed in the SB block group compared to the

Table 4. Intraoperative ETCO2 (mm HG) and SPO2 (%) changes of the studied groups.

Variables	Subtenon group (SB)(n = 40)	Intravenous group (IV)(n = 40)	*P*-value
Baseline SPO2	98 ± 0.8	98 ± 0.7	0.11
After induction ETCO2SPO2	37 ± 198 ± 0.7	36.7 ± 198.5 ± 0.7	0.0470.43
5 minutes ETCO2SPO2	35 ± 198 ± 0.4	35 ± 199 ± 0.38	0.60.03
10 minutes ETCO2SPO2	34 ± 0.998 ± 0.36	34.6 ± 0.9599 ± 0.57	0.0090.25
15 minutes ETCO2SPO2	33.8 ± 199 ± 0.2	33.9 ± 199 ± 0.4	0.90.48
20 minutes ETCO2SPO2	33.6 ± 0.8599 ± 0.3	34 ± 0.999 ± 0.45	0.30.76
25 minutes ETCO2SPO2	34 ± 0.899 ± 0.33	33.7 ± 0.799 ± 0.37	0.560.75
30 minutes ETCO2SPO2	33.6 ± 0.799 ± 0.4	33 ± 0.699 ± 0.4	0.180.28

Data are, mean± standard deviation (SD). ETCO2 end tidal CO2. $P < 0.05$ is considered statistically significant.

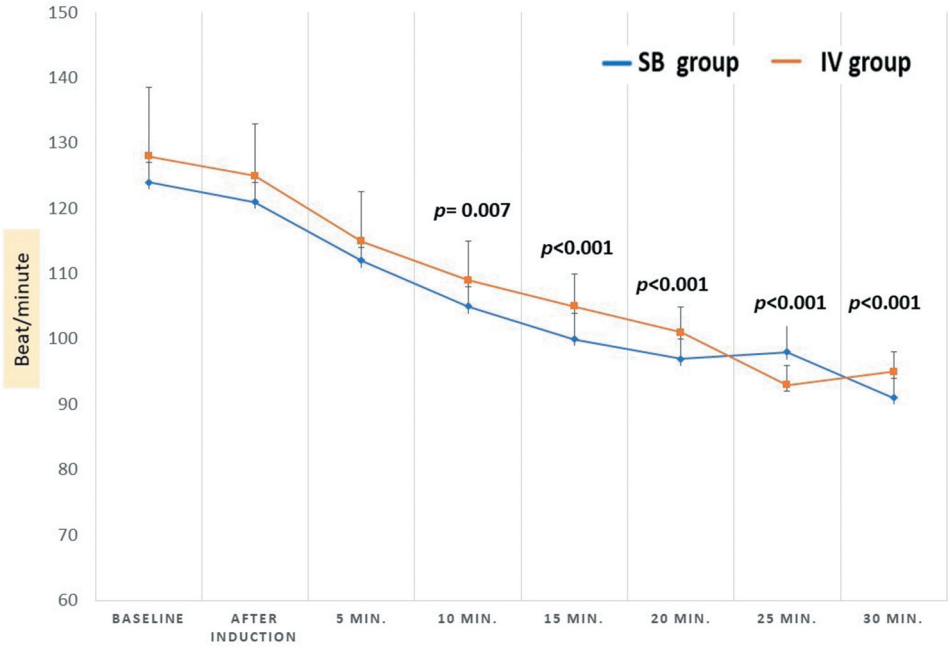

Figure 2. Intraoperative heart rate (Beat/minute) changes of the studied groups. Caption: Data are presented as mean± standard deviation. $P < 0.05$ is considered statistically significant.

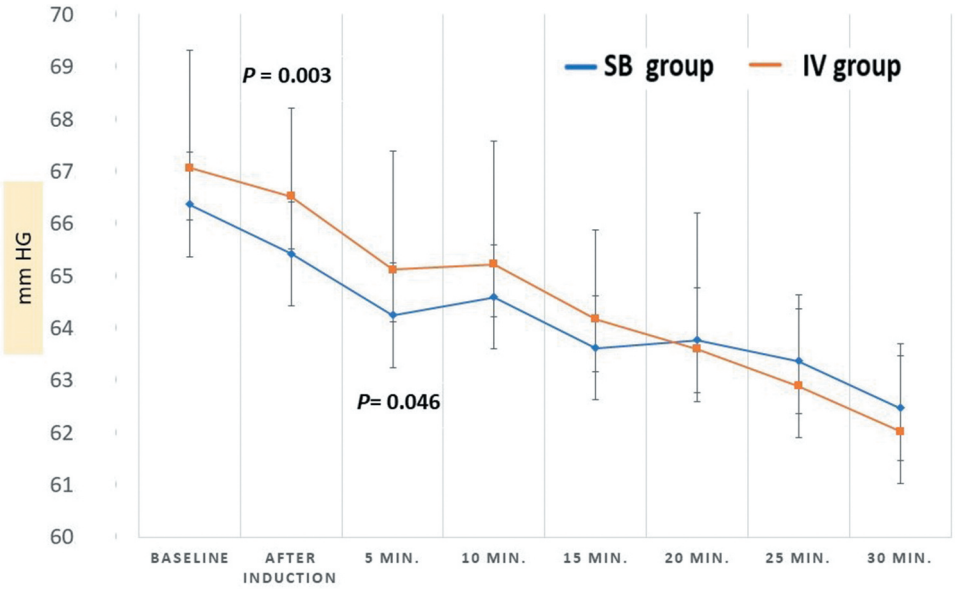

Figure 3. Intraoperative mean arterial blood pressure (mm Hg) changes of the studied groups. Caption: Data are presented as mean± standard deviation. $P < 0.05$ is considered statistically significant.

IV group. Otherwise, the incidences of vomiting and the need for antiemetics were comparable within the two groups.

To our knowledge, this is the 1st study used DEX as an adjuvant to bupivacaine 0.5% SB block and compared its effects to intravenous DEX in infants aged 1–12 months along with general anesthesia for cataract surgery. Additionally, a limited number of studies have evaluated SB block in conjunction with general anesthesia for pediatric ophthalmic surgeries [9–11].

On comparing different eye blocks in pediatric patients, SB appears to be more advantageous over peribulbar or retrobulbar blocks. Subtenon block seems to be the safest method of introducing anesthetic fluid into the retrobulbar spaces without the potential complication of blind sharp needle injection [12].

On the other hand, DEX is an alpha-2 agonist that has got numerous beneficial effects. It acts on both pre- and post-synaptic sympathetic nerve terminals and the central nervous system; thereby, decreasing the sympathetic outflow and norepinephrine release causing sedative, anti-anxiety, analgesic, sympatholytic and hemodynamic effects [13,14]. It is well evidenced that the use of IV dexmedetomidine can offer significant opioid-sparing effects [15]. When DEX is injected locally along with local anesthetics, it prolongs the duration of the block and postoperative analgesia. Dexmedetomidine infiltration as an adjuvant with local anesthetics has been frequently studied, e.g., in axillary, supraclavicular, and infraclavicular brachial plexus block, intrathecal, epidural and perineural blocks [13,14,16–19].

The results of our study agree with these previous studies which have reported better efficacy of adding dexmedetomidine as an adjuvant to subtenon block for cataract surgery in adults. For pediatric ophthalmic surgeries, a subtenon block accompanied by general anesthesia has been used only in a few studies [9–11].

We have utilized CRIES pain score because it has been established to be a reliable and valid useful scale of pain after surgery in infants [6,18]. Our findings agree with those reported by Ghai et al. [10] who compared subtenon blocks (group SB) with intravenous fentanyl (group F) in 140 children (6 months–6 years) undergoing cataract surgery under general anesthesia. The authors reported a significant reduction in the percentage of patients requiring rescue analgesia during the 24 hours in the SB group compared to the F group (29.3% versus 69.6%). In our study, we reported that the incidence of infants who required rescue analgesia was 5% in the SB group versus 27.5% in the IV group. The difference in results might be due to our shorter follow-up period (4 hours), the use of the CRIES score rather than the FLACC score used by Ghai et al., and the use of DEX in our interventions.

Steib et al. enrolled 50 adult patients who underwent strabismus surgery under general anesthesia and randomly divided them into two groups, 25 patients received SB bupivacaine block, and the other group was a control one. The incidence and severity of oculocardiac reflex was less in SB group and pain visual analog scale was lower [9].

The HR and MAP were significantly lower in the SB group compared to the IV group. The Significant decrease in HR and MAP from the baseline was reported in many studies when DEX was added to local anesthetics [13,14,19,20]. The decrease in HR and MAP caused by alpha-2 agonists can be explained

by its central action decreasing the sympathetic outflow and norepinephrine release.

Our findings regarding hemodynamic changes showed that the decrease was never exceeded 20% of the baseline values. This agrees with Bekker and coworkers, who studied the stability of hemodynamics when adding DEX to anesthesia in 72 patients undergoing craniotomy: either using sevoflurane-opioid anesthesia or sevoflurane-opioid-DEX anesthesia. They concluded that the addition of DEX to anesthesia has not increased the incidence of bradycardia or hypotension [21].

The reduction of respiratory rate within SB block group infants compared to the IV group was statistically significant but with no clinical significance and was not exceeded 20% of the baseline value. It could be explained by the adequate intraoperative analgesia. Generally, it is well known that DEX has minimal effects upon the respiration [4,22].

Previous studies regarding SB in children did not reveal complications related to the block technique [9–12] and we did not encounter any complication related to SB technique. Sheard et al. [23] mentioned that there is no anatomical reason that subtenon injection in children including infants should be more dangerous than in adults.

Our study was limited by the lack of a control group and the follow-up period was of short duration.

6. Conclusion

Subtenon block with a mixture of 0.05 ml/kg of 0.5% bupivacaine and 0.5 ug/Kg dexmedetomidine as adjuvant offers advantages of being safe and more effective for postoperative analgesia over intravenous dexmedetomidine in infants undergoing cataract surgery.

Author contribution

Dr. Wesam Nashat Ali helped by having full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Jehan Ahmed Sayed Bakr helped by taking responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Maram Amir helped and Marwa Abdelrady by designed the study protocol and data collection.

Dr. Mohammed Omar helped by doing all surgical interventions.

Dr. Emad Zarief Kamel helped by managing the statistical analysis literature searches and summaries of previous related work and wrote the first draft of the manuscript.

Disclosure statement

All authors have no conflicts of interest to report. All the authors of the manuscript received any remuneration. Further, the authors have not received any reimbursement or honorarium in any other manner. All the authors are members of the Faculty of Medicine Assiut University and practicing interventional pain physicians.

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