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Levobupivacaine versus levobupivacaine – dexmedetomidine for ultrasound guided bilateral superficial cervical plexus block for upper tracheal resection and reconstruction surgery under general anesthesia

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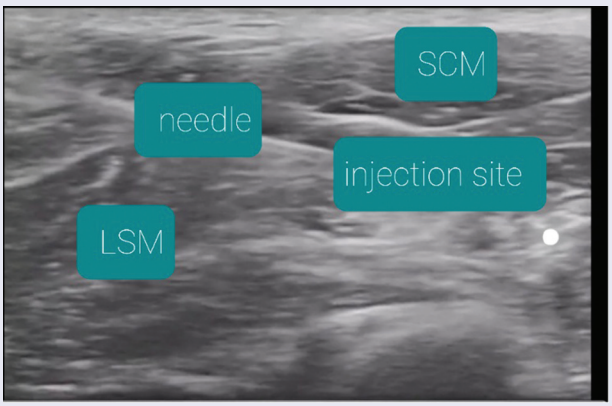
ABSTRACT

Background: Anesthesia for repair of tracheal stenosis considered as a challenging that needs to optimize the immediate postoperative period and preventing unwise use of postoperative opioid. This study was designed to evaluate the analgesic efficacy of adding dexmedetomidine to levobupivacaine for blocking the superficial cervical plexus for tracheal reconstruction.

Methods: Eighty patients, underwent elective surgical repair of upper tracheal stenosis and reconstruction. Patients were randomly allocated into two groups and received ultrasound guided bilateral superficial cervical plexus block. Group L received 10 ml of 0.5% Levobupivacaine. Group D received 10 ml of 0.5% Levobupivacaine and 0.5 µg/kg dexmedetomidine in each side. The total postoperative analgesic consumption, postoperative pain severity and the time to the first analgesic requirement were evaluated in all patients.

Results: Total postoperative fentanyl consumption decreased in group D (76.75 ± 9.57 µg) versus (176.75 ± 22.66 µg) in group L with p value ≤ 0.001 and time to first analgesic requirement was longer in group D (20.70 ± 5.42 hours) versus (8.35 ± 2.55 hours) in group L. Moreover, increased plasma cortisol level during surgery and after recovery in group L compared with group D with p value ≤ 0.001.

Conclusion: : Addition of dexmedetomidine to levobupivacaine for bilateral superficial cervical plexus block considered as an effective and safe block that significantly reduced total postoperative opioid consumption and prolonged time to first postoperative analgesic request with achievement of good quality of analgesia.



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Dexmedetomidine; superficial cervical plexus block; tracheal resection

1. Introduction

Tracheal stenosis after prolonged intubation period is the common indication for tracheal stenosis repair and reconstruction (TRR) surgeries which considered the main surgical procedure [1]. The time of emergence, extubation time, and postoperative maintaining neck flexion considered as a challenging stage of the operation that needs to avoid occurrence of agitation during emergence, vigorous neck extensions or severe coughing [2].

The use of combination of general anesthesia with regional anesthesia such as bilateral blocking the superficial cervical plexus (BSCP)may decreased the dose of general anesthesia [3]. In addition, it may provide good quality of postoperative analgesia and it can also reduce postoperative opioid analgesic requirement [4].

Levobupivacaine, is "S"-enantiomer of local anesthetic bupivacaine, but it is safer alternative for use in regional anesthesia technique than bupivacaine and

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equally effective analgesic as bupivacaine when used either bolus dose or continuously postoperative infusion [5].

Dexmedetomidine is a highly selective α2 agonist characterized by increased affinity to α2 adrenergic receptors while it has less α1, that responsible for its hypnotic and analgesic effects [6]. Several studies evaluated the analgesic efficacy of adding dexmedetomidine to bupivacaine either in experimental or in the clinical studies [7–11].

There were less published studies that evaluating the efficacy of adding levobupivacaine to dexmedetomidine for block of the superficial cervical plexus. The authors of the current study hypothesized that addition of dexmedetomidine to levobupivacaine for superficial cervical plexus block may provide good quality of postoperative analgesia for tracheal resection and reconstruction surgery.

The purpose of this current study was the evaluation of analgesic efficacy of addition of dexmedetomidine to levobupivacaine for blocking the superficial cervical plexus for repair of tracheal stenosis and reconstruction surgery with the total postoperative fentanyl consumption as a primary outcome.

2. Materials and methods

The current randomized, prospective, double-blind, controlled study was conducted at Mansoura University Hospital (Oto-Rhino-Laryngology anesthesia unit) after taken a Written informed consent from eighty patients with ASA 1 and II of either sex aged between 18- and 40-year olds and they were scheduled for surgical repair of moderate to severe upper tracheal stenosis and reconstruction surgery after prolonged intubation period. The current study was approved from the Institutional Research Board (IRB) of Mansoura University (R /17.09.19) and it was registered at clinical trial (NCT03426527) .

2.1. Exclusion criteria

We excluded from the study patients' refusal to participate in the study, patients with local infection at site of needle entry, coagulopathy, renal, cardiac, hepatic diseases, and pregnancy, patients who were unable to cooperate with the study protocol and pain scale assessment and known allergy to the study drugs.

2.2. Randomization and allocation concealment

After anesthesia was induced and before start of surgery, all patients undergone bilateral superficial cervical plexus block according to patients assignment by using generated randomization code in software with closed envelope) into two groups (40 patient for each group) group L (40): Received bilateral superficial cervical plexus block using ultrasound guided technique with 10 ml of 0.5% Levobupivacaine in each side and to achieve blindness saline was added with the same volume of dexmedetomidine.

group D (40): Received bilateral superficial cervical plexus block with 10 ml of 0.5% Levobupivacaine and 0.5 μg / kg dexmedetomidine in each side [12].

2.3. Anesthesia protocol

Preanesthetic checkup of all patients was done on the day prior to surgery. The study procedures had been explained to all patients and visual analogue scale (VAS) for evaluating pain was explained to all patients (100 mm unmarked line at which 0 = no pain while 100 mm = worst degree of pain imaginable). At the night of the surgery 5 mg oral diazepam was given to all participants and patients were informed for being fasting prior to surgery for 6 hours.

In the anesthesia room hemodynamic parameters as heart rate (beat /minute), systolic and diastolic blood pressure (mmHg) and oxygen saturation (SaO_2) were recorded . An intravenous 18 G cannula was inserted and intravenous infusion of Ringer's solution was started and all patients undergone general anesthesia with intravenous fentanyl 1 μg/kg, propofol 2 mg/kg and for tracheal intubation atracurium 0.4 mg/kg was used and endotracheal intubation was done according to the site of tracheal stenosis. If the lesion was distal to the larynx an endotracheal tube tip (ETT) was placed above the lesion while if the lesion proximal to the airway a narrow tube was inserted and if the patient was tracheostomised positive pressure ventilation through ETT was inserted into distal tracheal stump.

Anesthesia was maintained with minimum alveolar concentration (1MAC) of isoflurane with 50% oxygen and air. The patient's lungs were ventilated with positive pressure ventilation to maintain end-tidal carbon dioxide around 35 mmHg. Atracurium was given according anesthetist recommendation at increment doses of 0.1–0.2 mg/kg . Isoflurane concentration was increased and additional dose of intravenous fentanyl 0.5 μg/kg were injected if systolic blood pressure and/or heart rate increased 20% more than the baseline for 5 minutes or more with surgical stimulation after exclusion of other causes of tachycardia and hypertension.

3. Technique of superficial cervical plexus (SCP) block

Under guidance of ultrasound machine (PHILIPS CLEAR VUE 350), the superficial cervical plexus was performed by an anesthetist not involved in the study protocol after induction of anesthesia and before start of

surgery with all patients positioned at supine position with the head turned to either side with complete aseptic technique and using in plane approach to (SCP) with the ultrasound transducer (L12-4,Active Array) directional marker is medial then the superficial linear transducer was placed across the anterior of the neck with a transverse orientation at the level of the midpoint of the line connecting the mastoid process with the insertion of the sternal head of sternocleidomastoid muscle (SCM). Needle insertion was done at the SCM posterior border at the level of the cricoid cartilage and then needle advancement continued underneath sternocleidomastoid belly from lateral to medial direction toward the carotid artery where the cervical plexus appeared as a small collection of hypo echoic nodules then once the plexus was visualized the needle tip was positioned to inject the study drugs (according to the group allocation) deep to the posterolateral border of the SCM and superficial to the prevertebral fascia just above the levator scapulae muscle after negative aspiration with avoidance of deep injection [13] .

Continuous intraoperative monitoring of hemodynamic parameters as heart rate, systolic and diastolic blood pressure, oxygen saturation (SaO2) and end-tidal CO_2 were recorded every 15 minutes intraoperative till the end of surgical procedure and recorded values were averaged every hour of surgery to give a single mean value. At the end of surgery all anesthetics were discontinued and antagonization of residual neuromuscular block was achieved with neostigmine 40 µg/kg and atropine 20 µg/kg. Extubation time (from stoppage of inhalational anesthesia till extubation) and duration of surgery were recorded. Data collection was performed by another anesthetist not involved in the study protocol.

3.1. Post-operative assessment

After recovery all patients were immediately transferred to the postanesthesia care unit (PACU).

3.2. Primary outcome

The total dose of postoperative fentanyl consumption was recorded in the first postoperative 24 hours .

3.3. Secondary outcome

The time (hours) to first postoperative analgesic request was recorded and Ramsay sedation score was recorded immediately after extubation, 15 minutes after extubation and 30 minutes after extubation [14]. Blood samples were collected for assessment of the hormonal stress response to surgery including serum cortisol level (µg/dl) at basal value before induction of anesthesia, at one hour after the block and at one hour postoperative. Postoperative pain was assessed with the VAS at 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after surgery. Hemodynamic parameters as heart rate, systolic and diastolic blood pressure, and SaO_2 were recorded after one and two hours postoperative.

Postoperative analgesia was provided with intravenous ketorolac 30 mg/6 hour for all patients and if the VAS value continued to be > 30 an intravenous fentanyl 0.5 µg/kg was available as rescue analgesia and repeated after 4 hours from the previous fentanyl dose. Adverse systemic effects related to the block such as local anesthetics toxicity including (hypotension, seizures, arrhythmia, or conduction disorder), bloody taping, CSF aspiration, bleeding at puncture site, nausea, vomiting, Horner syndrome, hoarseness of voice, nerve injury, and ecchymosis were also reported.

Follow-up and data collection of patients were done by an anesthetist who not aware of the study protocol .

3.4. Sample size calculation and statistical analysis

Sample size was calculated by using t test for mean in G *power 3.0.10 program. According to pilot study using total postoperative analgesic consumption as primary outcome and with assuming type I error protection of 0.05 and using an effect size convention of 0.79 so the total sample size of 34 patients for each group and we added 6 cases in each group to compensate for patients dropped through the study. So, the total number of patients in each group was 40 patients in each group. Statistical analysis of data was done by using the Statistical Package of Social Science program for Windows Standard version 21 (SPSS). The normality of data was tested using one-sample Kolmogorov-Smirnov test . Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data and two groups were compared with Student *t* test. *p* value considered significant if ≤ 0.05 .

4. Results

Eighty patients of both sex aged between 18 and 40 years were allocated randomly into two groups (40 patients in each) and completed this randomized clinical trial (Figure 1). Patients' demographic data were comparable in both groups and there was no significant difference in both studied groups as regard the duration of surgery meanwhile extubation time between the studied groups showed significantly

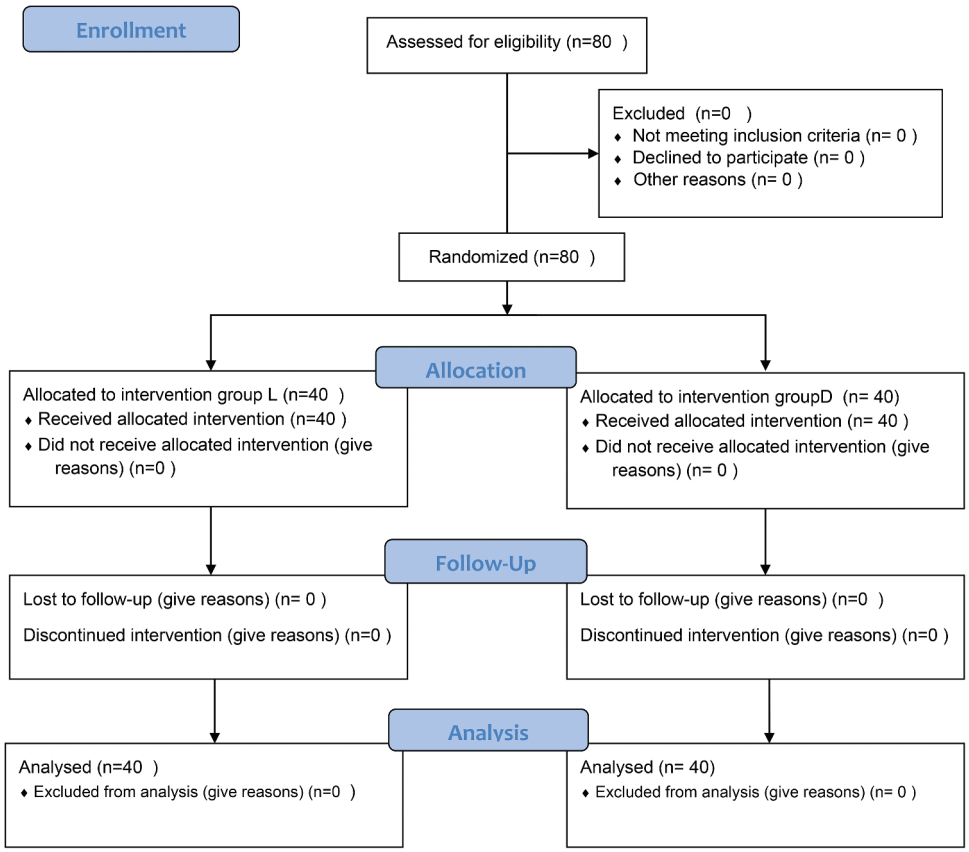

Figure 1. Consort flow diagram of patient progress through the randomized trial.

Table 1. Patient's characteristics, duration of surgery (hours) and extubation time (minutes) . Data expressed as mean ± standard deviation, numbers and percentage.

Variable	Group L (n = 40)	Group D (n = 40)	*p* value
Age (years)	24.25 ± 4.16	24.05 ± 3.92	0.826
Gender	25 (62.5%)	27 (67.5%)	0.639
Male	15 (37.5%)	13 (32.5%)	
Female			
Height (cm)	167.05 ± 3.42	166.92 ± 3.43	0.871
Weight (kg)	77.20 ± 6.19	78.42 ± 5.86	0.366
Body mass index (BMI) (kg/m^2)	27.69 ± 2.44	28.19 ± 2.50	0.373
Duration of surgery (hours)	4.24 ± 0.21	4.27 ± 0.22	0.616
Extubation time (min)	9.22 ± 0.73	11.15 ± 0.86	≤0.001*

Group L: levobupivacaine group
Group D: levobupivacaine – dexmedetomidine group
p value considered significant if ≤ 0.05 .
* Statistical significant differences among the studied groups

prolonged time in group D (11.15 ± 0.86 min) in comparison to group L (9.22 ± 0.73 min) with *p* value ≤ 0.001 as shown in Table 1 and the 95% confidence interval was (1.6–2.3). As regard the total postoperative fentanyl consumption it was found to be lower in group D (76.75 ± 9.57 µg) versus group L 176. 75 ± 22.66 µg with *p* value ≤ 0.001 with 95% confidence interval shown in Table 2 also the time for the first analgesic request a significantly prolonged time of effective analgesia (VAS < 30) was encountered in group D (8.35 ± 2.55 hours versus 20.70 ± 5.42 hours in group L with *p* value ≤ 0.001 with 95% confidence interval shown in Table 2. For Ramsay sedation score at extubation, at 15 minutes and at 30 minutes after extubation it showed increased score of sedation in group D in comparison lower values in group L with 95% confidence interval shown in Table 2.

As regard the plasma level of cortisol, the basal values achieved no significant difference in both groups but plasma cortisol level during surgery and after recovery in group L was increased significantly in comparison to the group D with *p* value ≤ 0.001 and with 95% confidence interval shown in Table 2.

Meanwhile in comparison with group L a significantly lower postoperative VAS was noticed in group D throughout 24 hours postoperative at one hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after surgery with *p* ≤ 0.001 (Figure 2).

Regarding hemodynamic parameters group D in comparison with group L reported significantly lower heart rate (beat/minute) values during intraoperative period and for one hour and 2 hours post operative with *p* ≤ 0.001 (Figure 3). While in systolic blood-(mmHg) pressure in both studied groups showed perioperative hemodynamic stability with no significant differences between both groups (Figure 4) also diastolic blood pressure (mmHg) values showed perioperative hemodynamic stability with no significant differences between both groups (Figure 5). No significant differences were observed as regard end-tidal CO_2 and SaO_2 throughout the study period between both studied groups.

Table 2. Total postoperative fentanyl consumption (µg). First postoperative analgesic request (hours). Perioperative serum cortisol level (µg/dl) . Ramsay sedation score at extubation, 15 and 30 minutes after extubation. Data expressed as mean ± standard deviation with 95% CI.

Variable	Group L (n = 40)	Group D (n = 40)	*p* value	95% CI
Total fentanyl consumption (µg)	176.75 ± 22.66	76.75 ± 9.57	≤0.001*	92.2–107
First postoperative analgesic request (hours)	8.35 ± 2.55	20.70 ± 5. 42	≤0.001*	10.5–14.2
Serum cortisol level basal (µg/dl)	33.87 ± 2.00	34.00 ± 1.97	0.779	0.76–1.01
Serum cortisol 1 hour after block (µg/dl)	24.67 ± 1.60	20.65 ± 1.91	≤0.001*	3.2–4.8
Serum cortisol 1 hour postoperative (µg/dl)	25.10 ± 1.51	20.92 ± 1.42	≤0.001*	3.5–4.8
Ramsay sedation score at extubation	3.67 ± 0.47	5.50 ± 0.50	≤0.001*	1.6–2.04
Ramsay sedation score 15 minutes after extubation	2.72 ± 0.50	4.87 ± 0.68	≤0.001*	1.9–2.4
Ramsay sedation score 30 minutes after extubation	1.90 ± 0.44	4.30 ± 0.46	≤0.001*	2.2–2.6

Group L: levobupivacaine group
Group D: levobupivacaine – dexmedetomidine group
p value considered significant if ≤ 0.05 .
* Statistical significant differences among the studied groups
95% CI: 95% confidence interval among the studied groups.

The majority of patients 36/40 (90%) in the group L received intraoperative a dose of fentanyl 0.5 µg/kg to attenuate the intraoperative increase in the heart rate and the blood pressure. Meanwhile none in the group D received additional intraoperative fentanyl. No serious adverse effects due to the SCP block were reported during the study period. As regard hoarseness of voice it was noticed in the early four hours postoperatively in two patients in each group without clinical significant differences . Moreover, three patients in group L and four patients in group D were reported complaining of nausea while four patients in each group were reported complaining of vomiting, all patients that complaining of nausea and vomiting were treated effectively with intravenous metoclopramide 10 mg .

5. Discussion

The current randomized prospective controlled double-blind study suggested that addition of dexmedetomidine to levobupivacaine for bilateral superficial cervical plexus nerve block was safe and effective that not only provided better analgesia but also reduced total postoperative fentanyl consumption in addition to attenuation of intraoperative and postoperative hormonal stress responses in patients undergoing tracheal resection and reconstruction surgery under general anesthesia.

Anesthesia for repair of tracheal stenosis and reconstruction surgeries not only needs understanding the surgical procedures, but it needs also cooperation with the surgical team specially with surgical manipulations at the airway during resection and anastomosis and also the management of emergence and postoperative care [15]. So it is important to use techniques that optimize the immediate postoperative period and preventing too early or too late extubation and unwise use of postoperative opioid that results in immediate loss of the airway patency which increases the risk of reintubation but with difficult situation or it may lead to performance of emergent tracheostomy. As the superficial cervical plexus supplies the skin of the

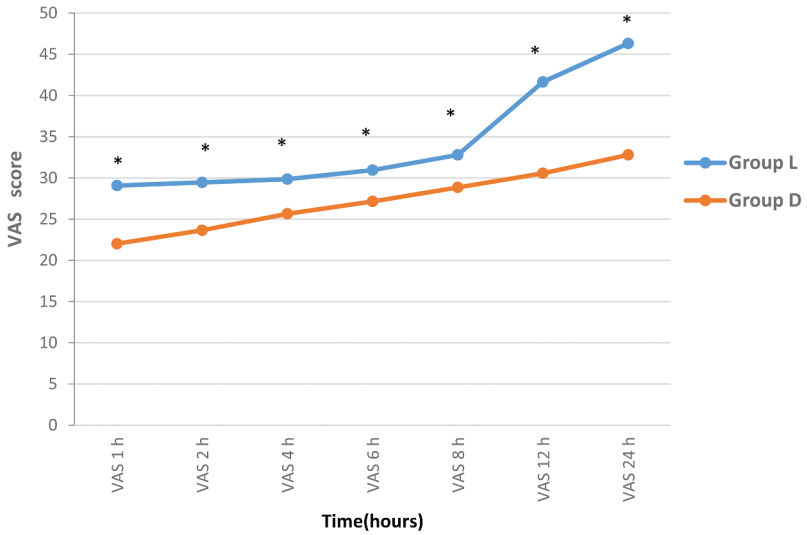

Figure 2. Visual analog score (VAS) at 1, 2, 4, 6, 8, 12, and 24 hours postoperative among studied groups. Group L: levobupivacaineGroup D: levobupivacaine – dexmedetomidine* Statistical significant differences among the studied groups

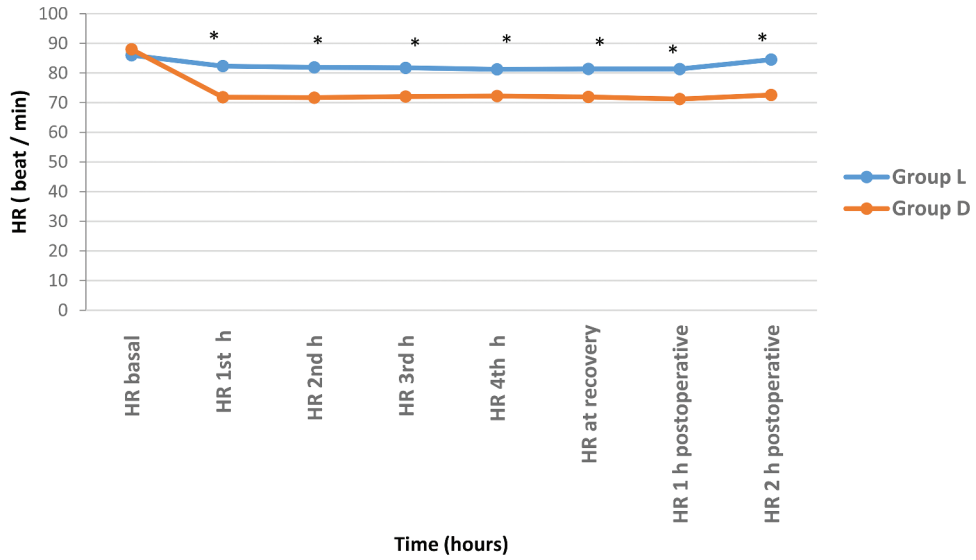

Figure 3. Heart rate (HR) beat/minute at basal value, 1st hour, 2nd hour, 3rd hour, and 4th hour intraoperative, at recovery, 1 hour postoperative and 2 hours postoperative. Group L: levobupivacaineGroup D: levobupivacaine – dexmedetomidine* Significant differences among the studied groups

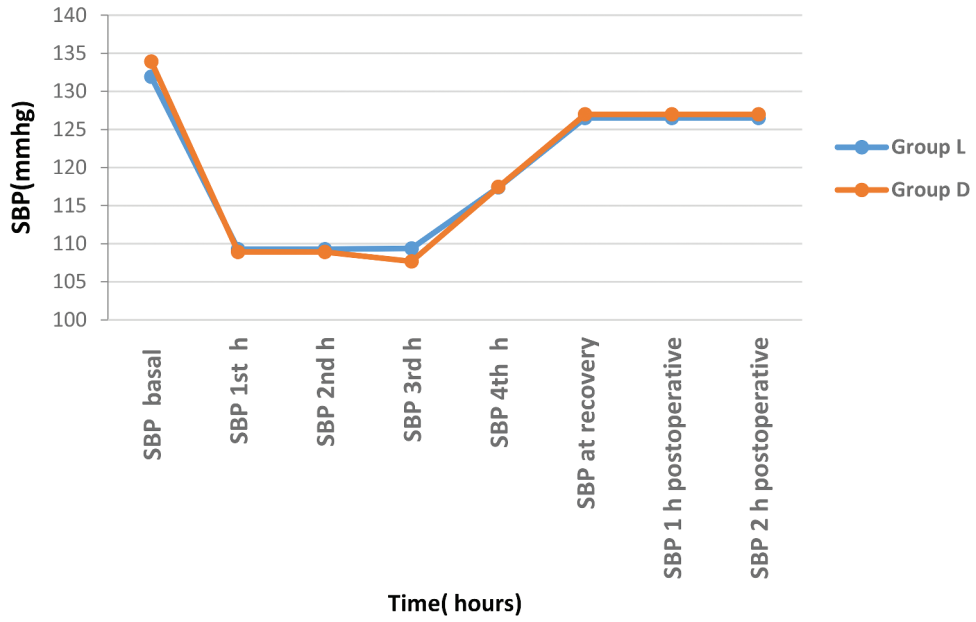

Figure 4. Systolic blood pressure (SBP) mmHg at basal value, 1st hour, 2nd hour, 3rd hour, and 4th hour intraoperative, at recovery, 1 hour postoperative and 2 hours postoperative with no significant differences among the studied groups. Group L: levobupivacaine, Group D: levobupivacaine – dexmedetomidine

anterolateral neck via the anterior primary rami form the second to fourth cervical nerves so the SCP block considered as one of the techniques that causes anesthesia of the anterior triangle of the neck.

Several studies has been evaluated the efficacy of using adjuncts to the local anesthetics in regional anesthesia to improve the quality of nerve blocks such as α2 agonists as adjuncts to local anesthetics and reported that it improved the analgesia and extended the block duration and they explained the mechanisms through producing vasoconstriction, central analgesia, and anti-inflammatory effects [16–18].

Dexmedetomidine considered as a highly selective α2 adrenergic receptor agonist, which have site of action in the brainstem locus coeruleus. It has also central antisympathetic function it produces analgesic and anxiolytic effects otherwise it may causes slight respiratory depression. So it is now widely used as a sedative in the intensive care unit and anesthesia especially in regional anesthesia [11].

Effects of using dexmedetomidine as adjuncts to local anesthetics on neuraxial and peripheral nerve blocks have been described by several studies [17,19]; however, no available studies were performed to

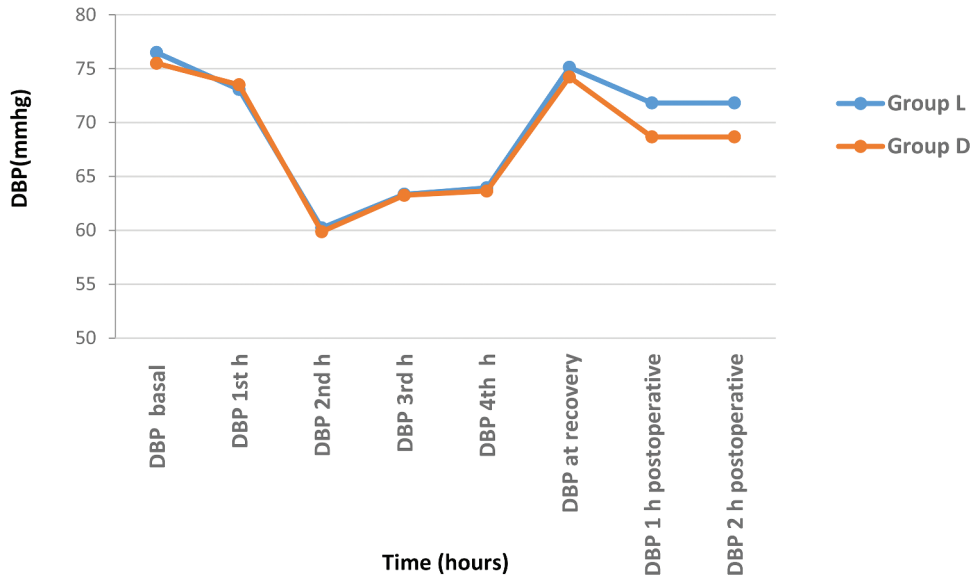

Figure 5. Diastolic blood pressure (DBP) mmHg at basal value, 1st hour, 2nd hour, 3rd hour, and 4th hour intraoperative, at recovery,1 hour postoperative and 2 hours postoperative with no significant differences among the studied groups. Group L: levobupivacaine, Group D: levobupivacaine – dexmedetomidine

evaluate the effect of adding dexmedetomidine to levobupivacaine for superficial cervical plexus block in patients undergoing tracheal stenosis repair and reconstruction surgery .

In the current study decreased total postoperative fentanyl consumption throughout the postoperative 24 hours together with prolonged time for first postoperative analgesic consumption also VAS scores of group D showed statistically significant lower values than those of the group L throughout 24 hours postoperatively in patients received dexmedetomidine with levobupivacaine for SCP block group, which may suggest the capacity of preincision SCP block with mixture of dexmedetomidine and levobupivacaine in disrupting the pain cycle without causing any adverse effects to patients this is in agreement with the results of the study by Lin et al. [20] who reported that addition of dexmedetomidine to local anesthetic ropivacaine for cervical plexus block decreased onset time of sensory block with prolonged duration of analgesia and improved the quality of analgesia, also another study by Kaygusuz et al. [21] concluded that dexmedetomidine when added to the axillary brachial plexus block could shortens the onset time of sensory block with increased the sensory and motor block duration and prolonged the time to take first analgesic request with reduction of total opioid consumption used without causing any adverse effects.

The magnitude and duration of hormonal stress response to surgery through sympathetic stimulation and activated secretion of hypothalamic-pituitary-adrenal axis is affected by surgical trauma leading to elevation of plasma cortisol from the adrenal cortex which can be inhibited through general anesthesia and regional anesthetic techniques [22]. The anticentral sympathetic effect of dexmedetomidine and activation of the vagus nerve, which led to decrease the plasma catecholamine levels which can provides intraoperative hemodynamic stability with decreased hormonal stress response to surgery which was achieved in the present study through reduction of the intraoperative and postoperative plasma cortisol and displayed perioperative hemodynamic stability and decreased heart rate in group D this results was parallel to the result of study by Elmaddawy and Mazy [23].

Lin et al. [20] in their study they found more hypotension, bradycardia, and sedation with 1 mcg/kg dexmedetomidine while in the present study hemodynamic stability was achieved to some extent and this may explained by using 0.5 mcg/kg in the present study.

Inadvertent deep injection of local anesthetics considered the major complication of the SCP block that leads to block the deeper neural structures but in the current study SCP block was done under direct ultrasound visualization of the needle tip during injection of local anesthetic that can easily avoid the occurrence of complications such as Horner syndrome due to involvement of sympathetic chain of the cervical region and affection of recurrent laryngeal nerve that leads to temporary hoarseness of voice [24]; however, in the current study only two patients in each group who suffered hoarseness of voice which resolved few hours postoperative and this is in agreement with the incidence in the study by Calderon et al. [25] who found that the incidence of both Horner syndrome

and hoarseness of voice was about 4% with using ultrasound guidance for SCP block for carotid endarterectomy; moreover, in the current study no one of patients complained of any difficulty of breathing due to affection of phrenic nerve and these results were in agreement with the results of study by Elmaddawy and Mazy [23] who observed that ultrasound-guided bilateral SCP block provided more prolonged analgesia with reduction of post-operative opioid consumption with less side effects during thyroid surgery.

Regarding postoperative nausea and vomiting we observed in the current study that there was no clinical significance between both the studied groups while Suh et al. [26] reported reduction of the incidence of nausea and vomiting in their study. However other studies reported that bilateral SCP block was not effectively decreased nausea and vomiting [27].

In conclusion, current study suggested that addition of dexmedetomidine to levobupivacaine for bilateral block of the superficial cervical plexus considered as an effective and safe method that not only significantly reduced total postoperative fentanyl consumption and prolonged time to first post-operative analgesic request but also provided good quality of analgesia in addition to attenuation of intraoperative and postoperative hemodynamic stress responses in patients undergoing tracheal resection and reconstruction surgery under general anesthesia.

Disclosure statement

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

Authors' contributions

Study design: Hanaa M. El Bendary,Ahmed M Abd El-Fattah, Hisham Atef Ebada, Salwa MS Hayes

Patient recruitment: Hanaa M. El Bendary, Salwa MS Hayes

Surgical procedure: Ahmed M Abd El-Fattah, Hisham Atef Ebada

Data collection and analysis: Hanaa M. El Bendary, Salwa MS Hayes

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