Original Article

Efficacy of peritonsillar infiltration with dexmedetomidine versus tramadol in comparison to placebo for pain control and sedation after tonsillectomy in pediatric patients: A randomized clinical trial

ABSTRACT

Objective: This article aimed to assess the efficacy of peritonsillar infiltration with dexmedetomidine-ropivacaine versus tramadol-ropivacaine for pain control and sedation after tonsillectomy in pediatric patients.

Materials and Methods: This double-blind clinical trial recruited 99 eligible children (4–8 years old) undergoing tonsillectomy and assigned to three block-randomized groups, receiving dexmedetomidine-ropivacaine (group A), tramadol-ropivacaine (group B), or placebo-ropivacaine (group C). The vital signs included blood pressure, heart rate, and SaO_2 before anesthesia induction, during surgery at regular intervals until 24 h after surgery. The duration of surgery and recovery, complications, and analgesic consumption were recorded and pain scores were measured by Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and Oucher scales as well as sedation scores by the Wilson sedation scale. Data were analyzed within SPSS 20 at a significance level of 0.05.

Results: The lowest pain scores were measured by the CHEOPS scale in the dexmedetomidine-ropivacaine group ($P < 0.05$). Statistically significant difference was observed in the CHEOPS pain score between the first two groups at 30 min, 1 h, 2 h, and 4 h after surgery ($P < 0.01$). The differences were revealed in the Oucher pain assessments among all groups from the time of recovery to four postoperative hours ($P < 0.05$), with the lowest in the dexmedetomidine-ropivacaine group whose sedation score was greater during recovery and 5 min after surgery ($P < 0.05$). Subjects in tramadol group had six cases of dizziness and nausea, while no side effects were observed in two other groups ($P < 0.05$). Only seven participants receiving dexmedetomidine required acetaminophen, but 29 in the tramadol group and all in the placebo group demanded to receive acetaminophen ($P = 0.001$).

Conclusion: The authors concluded that dexmedetomidine as an adjuvant to ropivacaine has better performance in local infiltration for intra- and post-tonsillectomy analgesia and postoperative sedation, without any special side effects (like the placebo group), and that it hence is recommended to be used for local infiltration during tonsillectomy.

Keywords: Dexmedetomidine, general anesthesia, pain control, peritonsillar infiltration, ropivacaine, sedation, tonsillectomy, tramadol

INTRODUCTION

Nowadays, a large portion of pediatric diseases and health-care costs remains to be accounted for by inflammatory and infectious diseases of the throat, tonsils, and adenoids, in most cases, leading to two common pediatric surgeries, that is, tonsillectomy and adenotonsillectomy.[1] The first treatment option for the disease is thought to be a common,

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painful procedure, associated with postoperative problems including pain, bleeding, laryngospasm, airway obstruction, nausea and vomiting, and aspiration.[2] Several analgesics are reported to be selected for post-tonsillectomy pain relief, like narcotics, non-steroidal anti-inflammatory drugs, and local anesthetics among which narcotics may contribute to the reduced tone of the upper airway, weakened cough reflex, respiratory failure, and postoperative nausea and vomiting.[3] Numerous studies have reported the beneficial effects of preoperative analgesia induced by different commonly used drugs for postoperative pain treatment.[4]

First, dexmedetomidine continues to be an 2-adrenergic agonist, with analgesic, sedative, and antihypertensive properties[5] and can be considered an effective treatment when added to local anesthetics during peripheral nerve block.[6,7] Tramadol is a synthetic opioid of the amino cyclohexanol group and a centrally acting analgesic with weak opioid agonist properties, which appears to have major effects on noradrenergic and serotonergic neurotransmission, whereas some data showed the efficacy of adding tramadol to local anesthetics for peripheral nerve blocks.[8] It is considered to be a centrally acting analgesic with two distinct mechanisms of action: weak agonist effects on μ-opioid receptors and neurotransmitter reuptake inhibitors.

The CHEOPS is a valid scale to assess the pain severity and mostly preferred for children of age group 1–5 years, but it is used in older children in some studies.[9,10] In addition, Oucher scale is a valid and reliable tool to measure the self-report pain measurement in all patients. We used these two pain measurement scales for assenting the pain score in this clinical trial.[11-14] Numerous trials showed that it helped relieve pain by intravenous and intramuscular administration.[15] As reported by another study on the efficacy of peritonsillar infiltration with tramadol on post-tonsillectomy pain relief, use of tramadol increased the risk of nausea and vomit between 2 and 6 h after surgery.[16] Though the importance of managing post-tonsillectomy pain has been cited in various studies using different pain-relieving drugs, but not our adjuvants, the present clinical trial was designed to compare the efficacy of peritonsillar infiltration of dexmedetomidine-ropivacaine versus tramadol-ropivacaine for pain control and sedation after general anesthesia tonsillectomy.

MATERIALS AND METHODS

Setting and patients

In a randomized, double-blind, parallel clinical trial, 99 pediatric patients with 4–8 years' old who undergoing tonsillectomy recruited. Sample size calculation and the required sample for each study group were calculated using the results of the study by our recent study[17] and considering the study power being equal to 80% as well as the confidence interval of 95% in each group equaling 33 patients.

The eligible subjects recruited based on inclusion and exclusion criteria. Inclusion criteria were patients aged 3 to 12, American Society of Anesthesiologists class II and I, undergoing tonsillectomy, and absence of chronic pain. Exclusion criterion was included patient or parents' dissatisfaction with the surgery and using analgesics. Moreover, patients with metabolic endocrine disease, coagulation disease, mental retardation, growth and development disorders, allergy to the drugs used, peritonsillar abscess, hypertension, and psychotic disorder were excluded from the study.

Intervention

All subjects were hospitalized at least one day before surgery and they were kept nil per os (NPO) for 8 h. After ensuring adherence to NPO guidelines and administration of 5 ml/kg IV crystalloid Ringer's solution, all patients underwent the same anesthesia protocol, receiving 1 μg/kg fentanyl, 5 mg/kg thiopental sodium (Jaber-Pharma Co., Karaj, Iran), and 0.5 mg/kg IV atracurium. Patients were randomized into three groups using a block randomization method [Figure 1]. After induction of anesthesia and endotracheal intubation by spiral cuffed ETT with appropriate size for each patient, and immediately before surgical incision, the tonsillar bed, and peritonsillar tissues were infiltrated on both sides using the same technique, with fanwise injections from the superior and inferior poles of the tonsillar fossa by a surgeon who performed surgery 5 min later. Dexmedetomidine-ropivacaine group (group A), receiving a 5-ml solution containing 0.25% ropivacaine + 1 μg/kg dexmedetomidine (Exir Pharmaceutical Co., Borujerd, Iran);[18] tramadol-ropivacaine group (group B), the same ropivacaine solution + 2 mg/kg tramadol (Caspian Tamin Co., Rasht, Iran);[10] and placebo-ropivacaine group (group C), the same solution + normal saline,[18] and all given by peritonsillar infiltration. To equalize the volume of the study drug administered to each subject, once the target dose of adjuvant was determined, it was diluted to 10 ml with distilled water, and then 5 ml of the prepared drug was infiltrated on each side. Local infiltration was used for administration of interventions including dexmedetomidine and tramadol as adjuvant.

Intravenous metoclopramide 0.1 mg/kg was administered to patients with vomiting or nausea. Furthermore, sedation score was recorded in recovery, 5, 15, and 30 min, as well as 1, 2, 4, 6, 12, and 24 h after surgery. To ensure the study blind is maintained, the patients and data collector intern were

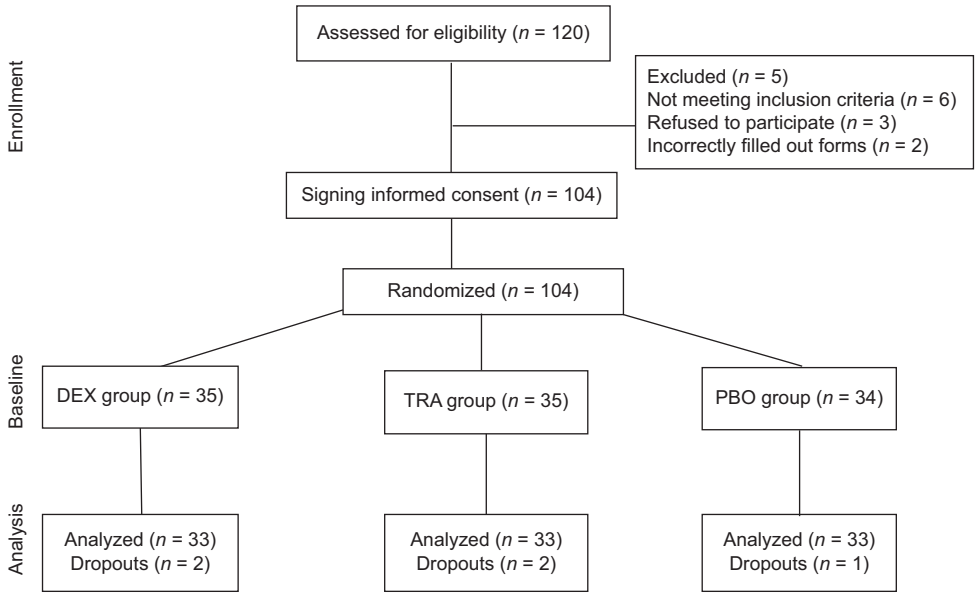

Figure 1: CONSORT diagram showing the flow of participants through each stage of a randomized trial

unaware of the group allocation, whereas an anesthesiologist administered general anesthesia and injected the drugs.

Measurements

We recorded the monitored patients' vital signs including mean arterial pressure (MAP), heart rate (HR), and saturation oxygen (SaO_2) before induction of anesthesia, at regular intervals during surgery, and in recovery time. The recovery time considered based on the Aldrete score and when the Aldrete score is achieved above 8, the patient is discharged from recovery as conducted in other studies.[19,20] The CHEOPS, Oucher, and Wilson scales were used for the pain severity assessment, self-report pain measurement, and sedation evaluation, respectively. The validity and reliability of pain and sedation assessment tools are shown in other studies.[2,12,13,19,21]

The reference point for measurement of pain score was started from entering to recovery room. The Oucher, a self-report pain assessment tool for children aged 3–12, is used by child health professionals worldwide, whose reliability has been documented, while statistical tests have established its content and construct validity.[13,22] Pain score was measured during recovery, 5, 15, and 30 min, 1, 2, 4, 6, 12, and 24 h after surgery. This tool is one of the most validated, oldest, and most widely used self-report measures of children's pain intensity, developed by Beyer[13,22] and comprises six photographs of a child's face showing different expressions of pain. It is oriented vertically and has numbers assigned to each face scored within the range of one (no pain) to 10 (worst pain), based on which doses of 10–15 mg/kg of acetaminophen in tablet form were used to relieve pain if the patients' pain exceeded five.

Ethical consideration

All patients and their parents were informed about the objectives of the study and signed the written informed consent. Ethical clearance was obtained from the Institutional Ethical Committee with Ref no IR.ARAKMU.REC.1400.040 dated 03.07.2018. Moreover, the protocol is registered in Iranian Registry Clinical Trial by code IRCT20141209020258N163.

Statistical analysis

Data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to assess the normal distribution of data. One-way analysis of variance (ANOVA) was used to analyze the mean difference of quantitative variables among three groups, and ANOVA was used to assess the difference between groups during time for repeated observations. The Chi-square test was applied to analyze the gender, complications, and analgesic consumption among the studied groups. A significant level was considered at 0.05.

RESULTS

This double-blind trial enrolled 99 pediatric patients undergoing tonsillectomy, who were randomly split into three groups (dexmedetomidine + ropivacaine, tramadol + ropivacaine, and placebo + ropivacaine) with minimum and maximum ages of 4 and 8 years; the overall mean age was 6.97 ± 1.45, among which 54 (54.5%) were men and 45 (45.5%) were women. No statistically significant difference was observed regarding SaO_2, MAP, HR, the duration of surgery, and Aldrete score ($P > 0.05$).

Statistically significant differences [Table 1] were seen among the groups in terms of CHEOPS scores across the study time points ($P < 0.05$), as confirmed by repeated measure ($P < 0.05$). The lowest pain score was observed in the dexmedetomidine-ropivacaine group. A statistically significant difference was found in pain scores between the two groups of dexmedetomidine and tramadol in 30 min, 1, 2, and 4 h after surgery ($P < 0.01$). Chart 1 depicted based on repeated measurements test and showed that there was a significant difference in trend of pain score among three groups and the lowest pain was reported in the dexmedetomidine-ropivacaine group ($P < 0.05$).

Based on Table 2, statistically significant differences were seen in Oucher scores among the groups from the time of recovery to 4 h after surgery ($P < 0.05$). As repeated measures test also confirmed, statistically significant differences were found in terms of Oucher scores in the groups ($P < 0.05$). The lowest pain score was observed in the dexmedetomidine-ropivacaine group. Statistically significant difference was observed in pain intensity measured by the Oucher scale between the two groups of dexmedetomidine and tramadol, whereas the pain score was less in the first group ($P < 0.05$). The repeated measurements test [Chart 2] showed that dexmedetomidine-ropivacaine group have different trend of pain with other groups.

Statistically significant differences were found in sedation [Table 3] among the three groups during recovery and 5 min after surgery ($P < 0.05$), while it was greater in the dexmedetomidine group at the two time points. Though statistically significant differences were observed among the groups in terms of complications (dizziness and nausea ($P = 0.002$), the tramadol group had six cases of dizziness and nausea, while no side effect was found in the dexmedetomidine group [Table 4]. Statistically significant differences [Table 5] were found in analgesic consumption among the groups ($P = 0.001$). Seven patients receiving dexmedetomidine needed acetaminophen, but 29 patients in the tramadol group and all those in the placebo group demanded to receive acetaminophen.

DISCUSSION

This double-blind trial recruited three groups of patients scheduled for tonsillectomy at the Amir Kabir Hospital (Arak), receiving dexmedetomidine-ropivacaine, tramadol-ropivacaine, or placebo-ropivacaine infusions, and showing no significant difference in SaO_2, HR, and MAP, as well as the duration of surgery. The lowest pain score measured by the CHEOPS scale was observed in the dexmedetomidine-ropivacaine group. Statistically significant difference was found in the CHEOPS pain assessments between the first two groups at 30 min, 1,

Table 1: Comparison of mean and SD of CHEOPS scores

Group CHEOPS scores	Dexmedetomidine-ropivacaine Mean±SD	Tramadol-ropivacaine Mean±SD	Placebo-ropivacaine Mean±SD	*P*
Recovery	0.242±0.435	0.303±0.466	0.818±0.682	0.001
5 min postop	0.393±0.496	0.545±0.616	1.30±0.636	0.001
15 min postop	0.393±0.496	0.666±0.478	1.42±0.560	0.001
30 min postop	0.393±0.496	1.09±0.291	1.57±0.501	0.001
1 h postop	0.606±0.496	1.21±0.415	1.57±0.501	0.001
2 h postop	0.787±0.415	1.36±0.488	1.66±0.478	0.001
4 h postop	1.15±0.364	1.42±0.501	1.75±0.435	0.001
6 h postop	1.45±0.505	1.48±0.507	1.78±0.415	0.009
12 h postop	1.42±0.501	1.39±0.496	1.78±0.415	0.001
24 h postop	1.42±0.501	1.39±0.496	1.78±0.415	0.001

Table 2: Comparison of mean and SD of Oucher pain scores

Group Oucher scores	Dexmedetomidine-ropivacaine Mean±SD	Tramadol-ropivacaine Mean±SD	Placebo-ropivacaine Mean±SD	*P*
Recovery	1.42±0.501	2.36±0.488	3.06±0.704	0.001
5 min postop	1.63±0.603	2.57±0.613	3.27±0.574	0.001
15 min postop	2.00±0.433	2.90±0.678	3.45±0.616	0.001
30 min postop	2.27±0.452	3.09±0.842	3.69±0.847	0.001
1 h postop	2.54±0.564	3.42±0.830	4.00±0.559	0.001
2 h postop	2.969±0.529	3.72±0.674	4.09±0.723	0.001
4 h postop	3.33±0.595	4.06±0.704	3.78±0.780	0.001
6 h postop	3.63±0.603	3.90±0.630	3.60±0.658	0.105
12 h postop	3.72±0.516	3.66±0.645	3.42±0.501	0.071
24 h postop	3.90±0.522	3.66±0.645	3.72±0.452	0.177

Table 3: Comparison of mean and SD of Wilson sedation scores

Group Wilson scores	Dexmedetomidine-ropivacaine Mean±SD	Tramadol-ropivacaine Mean±SD	Placebo-ropivacaine Mean±SD	*P*
Recovery	2.48±0.507	1.63±0.488	1.57±0.501	0.001
5 min postop	2.48±0.507	1.63±0.488	1.57±0.501	0.001
15 min postop	1.84±0.618	1.60±0.496	1.57±0.501	0.086
30 min postop	1.84±0.618	1.60±0.496	1.57±0.501	0.086
1 h postop	1.30±0.466	1.30±0.466	1.33±0.478	0.955
2 h postop	1.30±0.466	1.30±0.466	1.33±0.478	0.955
4 h postop	1.06±0.242	1.00±00.00	1.00±00.00	0.132
6 h postop	1.00±00.00	1.00±00.00	1.00±00.00	>0.05
12 h postop	1.00±00.00	1.00±00.00	1.00±00.00	>0.05
24 h postop	1.00±00.00	1.00±00.00	1.00±00.00	>0.05

Table 4: Comparison of frequency and percentage of complications (dizziness, hypotension, nausea, and bradycardia)

Group Complications	Dexmedetomidine-ropivacaine Number (%)	Tramadol-ropivacaine Number (%)	Placebo-ropivacaine Number (%)	*P*
Does not have	33 (100)	27 (81.81)	33 (100)	0.0020
Dizziness and nausea	0 (0)	6 (18.18)	0 (0)	

Table 5: Comparison of frequency and percentage of analgesic consumption

Group Analgesic consumption	Dexmedetomidine-ropivacaine Number (%)	Tramadol-ropivacaine Number (%)	Placebo-ropivacaine Number (%)	*P*
Does not have	27 (81.81)	4 (12.12)	0 (0)	0.001
Has	7 (21.21)	29 (87.87)	33 (100)	

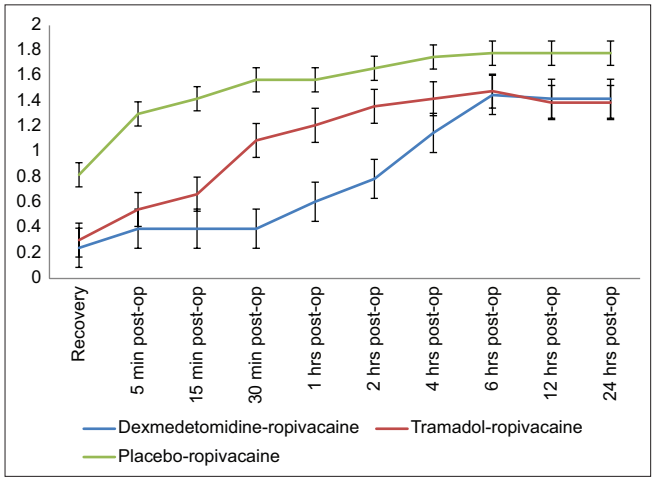

Chart 1: Comparison of pain assessed by the CHEOPS scale

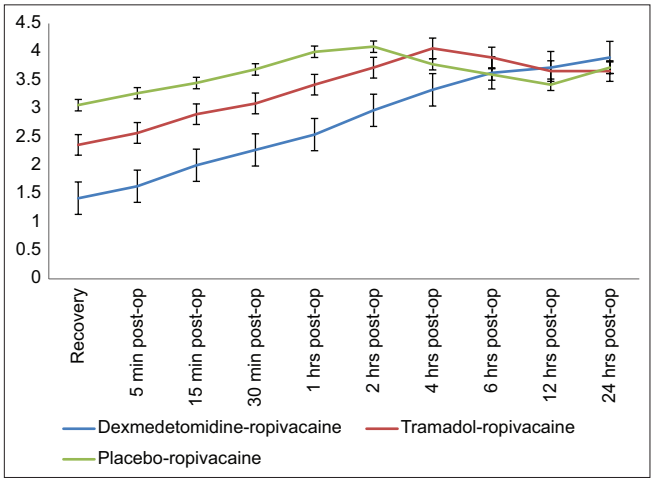

Chart 2: Comparison of pain intensity measured by the Oucher scale in the groups

2, and 4 h after surgery and in the Oucher pain assessments among the three groups from the time of recovery to 4 h after surgery, with the lowest in the dexmedetomidine-ropivacaine group. Moreover, a significant difference was found in pain intensity measured by the Oucher scale between the two groups of dexmedetomidine and tramadol, and the pain score was less in the dexmedetomidine group in which sedation score was greater during recovery and 5 min after surgery.

Moreover, statistically significant differences were observed in complications including dizziness and nausea among the groups. The tramadol group had six cases of dizziness and nausea, while no side effects were found in the dexmedetomidine group. Statistically significant differences were found among the three groups in terms of analgesic consumption. Only seven patients in the dexmedetomidine groups needed acetaminophen, while 29 patients in the tramadol group and all in the placebo group needed to receive acetaminophen. Overall, dexmedetomidine alleviated pain and increased sedation in patients without causing any side effects, while the

receiving patients needed the minimum analgesic dose within 24 h.

As an α2-adrenergic agonist, dexmedetomidine has analgesic, sedative, and antihypertensive properties[5] and can be effective if added to local anesthetics during peripheral nerve block.[6,7] Lahane *et al*.[23] compared the peritonsillar infiltration and intravenous dexmedetomidine for perioperative analgesia in tonsillectomy and concluded that peritonsillar dexmedetomidine medication can be a valuable alternative to intravenous dexmedetomidine. Similarly, our results indicate the significant efficacy of dexmedetomidine in relieving pain and increasing sedation. Similarly, Modir *et al.*'s[24] clinical trial assessed the efficacy of granisetron, dexmedetomidine, and lidocaine after etomidate injection for general surgery in which pain score was low in the intervention groups, and lower in the dexmedetomidine group, while the mean pain score was statistically less in the lidocaine group than granisetron, whose results were consistent with ours.

Alebouyeh *et al*.[25] performed a study evaluating the analgesic effect of topical tramadol on postoperative pain control in children undergoing tonsillectomy or adenotonsillectomy, suggesting that peritonsillar tramadol infiltration can be recommended as a safe method that creates appropriate analgesia in children undergoing tonsillectomy or adenotonsillectomy. The tramadol group in our study had better effectiveness than the placebo group, reduced pain, and increased sedation but had no better efficacy profile than dexmedetomidine. Tsaousi *et al.*'s[26] review explored the peritonsillar infiltration of tramadol and bupivacaine to improve the outcome of tonsillectomy in children and suggested that the infiltration can play an important role in pain relief and be recommended. Our trial showed that tramadol effectiveness was more than that of placebo but less than that of dexmedetomidine.

Similar to our finding, Heiba *et al.*'s[27] results from a study aimed at comparing peritonsillar infiltration of tramadol and lidocaine for the post-tonsillectomy pain relief indicated that the effect of tramadol in pain management during the first six postoperative hours was comparable to that of lidocaine. Moreover, Ayatollahi *et al*.[28] compared the peritonsillar infiltration effects of ketamine and tramadol on post-tonsillectomy pain, concluding that peritonsillar infiltration of tramadol reduces pain, analgesic consumption, and the time to recovery without any significant side effects. In our study, tramadol was more effective than placebo, while dexmedetomidine was more effective in reducing pain and increasing sedation. In line with our study, Abdel-Ghaffar and Abdel-Haleem[18] reported their finding on the effect of peritonsillar versus intravenous administration of dexmedetomidine on pediatric post-tonsillectomy pain relief, concluding that though both methods were effective for pain management and procedural sedation, peritonsillar infiltration is recommended because it has no systemic effects, improves family satisfaction, and increases the total oral fluids on the first day.

CONCLUSION

The three-group comparison indicated that dexmedetomidine as an adjuvant to ropivacaine has better performance in local infiltration for intra- and post-tonsillectomy analgesia and postoperative sedation, without any special side effects and that it hence is recommended to be used for local infiltration for tonsillectomy.

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Conflicts of interest

There are no conflicts of interest.

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