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A Randomised Controlled Trial to Assess the Analgesic Efficacy of Reduced Dose 0.2% Ropivacaine–Dexmedetomidine Combination Compared to Standard 0.375% Ropivacaine in USG Guided TAP Block for Paediatric Hernia Repair

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Abstract

Objective: Paediatric pain management has remained understated practice over a period of time. Recently ultrasound-guided (USG) guided techniques are gaining popularity for perioperative analgesia, especially in the paediatric population. So, the aim of the present study was to evaluate the efficacy of reduced dose ropivacaine–dexmedetomidine combination compared to standard 0.375% ropivacaine in USG guided transversus abdominis plane (TAP) block.

Methods: Sixty children of either sex, aged 2–10 years, posted for elective open herniotomy under general anaesthesia were randomly divided into two groups of 30 patients each. Group RD received 0.2% ropivacaine with dexmedetomidine 1 μg kg^{-1} while group R received 0.375% ropivacaine at 0.5 mL kg^{-1}. Meantime to first rescue and total analgesics, Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and Ramsay sedation score, haemodynamic parameters and adverse effects were noted.

Results: Time to first rescue analgesia in group RD and group R were 16.32 ± 3.11 hours and 10.82 ± 2.16 hours, respectively ($P < .0001$). Mean CHEOPS score were 4.48 ± 1.1 and 6.3 ± 1.74 ($P < .024$) in group RD and R. Post-op Ramsay sedation score was significantly greater in group RD. Heart rate and blood pressure remained similar in either of the group. No episode of respiratory depression, bradycardia or hypotension was noted perioperatively.

Conclusion: Combination of 1 μg kg^{-1} dexmedetomidine with reduced concentration of ropivacaine (0.2%) produced significantly longer duration of post-operative analgesia and lowered post-operative CHEOPS pain score in comparison with 0.375% ropivacaine alone in USG guided TAP block for paediatric hernia repair.

Keywords: Analgesia, child, dexmedetomidine, ropivacaine, ultrasonography, nerve block

Introduction

Perioperative pain relief is an essential component of modern anaesthetic practise that drastically reduces the stress response of surgery and perioperative morbidity leading to fast-tracking of the surgical patients.[1] Traditionally paediatric patients have been managed by intravenous analgesics and local infiltration. With the greater availability of ultrasonography (USG) in the recent era, a surge in the use of regional blocks is evident. Owing to their excellent pain relief and opioid-sparing effect, regional bocks are becoming the standard of care in many of the paediatric surgeries.

Transversus abdominis plane (TAP) block providing excellent analgesia from T6 to T12 dermatome has shown encouraging results in various upper abdominal surgeries. With the application of USG, TAP has become increasingly popular and safer in the paediatric population as it provides real time visualisation of anatomy and neural

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structures leading to a decrease in volume and concentration of local anaesthetic (LA) use compared to landmark technique.

Ropivacaine is the S-enantiomer of bupivacaine, having similar pKa but favourable toxicity profile compared to bupivacaine. The available evidence suggests comparable onset, quality and duration of the sensory block but with a less intense and shorter duration of motor block.[2] Given the requirement of a large volume of LA in TAP block, especially in paediatric patients, replacement of bupivacaine with ropivacaine appears prudent. Dexmedetomidine has been extensively used in adults as an adjuvant to LA in various nerve blocks. When administered as an adjuvant with LA in TAP block, dexmedetomidine inhibits the stress response and prolongs the duration of analgesia to approximately 150–175% in some studies.[3–5] However, the effect of dexmedetomidine on the potency of ropivacaine for USG guided TAP block in paediatric patients has not been investigated considerably.

Hence, the present study is designed to evaluate the effectiveness of dexmedetomidine as an adjuvant in reducing the concentration of ropivacaine with the hypothesis that analgesia provided by combination of 1 μg kg^{-1} of dexmedetomidine and 0.2% ropivacaine is inferior to 0.375% ropivacaine alone in USG guided paediatric TAP block.

Methods

Following approval from JNMC institutional ethics committee, written informed consent from parents, this prospective, randomised, double-blind, controlled, parallel, non-inferiority trial was conducted in a tertiary care hospital over a period of 1 year (2019-2020) on 60 children of either sex, aged between 2 and 10 years posted for elective open herniotomy under general anaesthesia. Patient with any contraindications to TAP block like surgical scar or distorted anatomy at the site of injection, known allergy to local anaesthetics and children with known cardiovascular, respiratory, hepatic or renal disease were excluded. Patients were randomly divided into two groups of 30 patients each (group R and group RD) on the basis of computer generated random number table. Group R received 0.5 mL kg^{-1} 0.375% ropivacaine (dilution of 1:1 sterile water and ROPIN® 0.75%; Neon Laboratories Ltd.), while group RD received 0.5 mL kg^{-1} 0.2% ropivacaine (ROPIN 0.2%; Neon Laboratories Ltd.) with dexmedetomidine 1 μg kg^{-1} in unilateral TAP block (Figure 1). The allocations were concealed in the sequentially numbered opaque envelopes opened just prior to anaesthesia. The patients and the investigator were blinded to the intervention. All drugs were loaded by an anaesthetist who did not have any involvement in further patient assessment, while anaesthesia was administered and assessed by different anaesthetist.

Main Points

- Dexmedetomidine is known to have synergistic effect with local anaesthetics.
- Ropivacaine 0.375% is commonly used concentration in transversus abdominis plane block but margin of safety is a major issue in paediatric patients.
- Reduced dose of ropivacaine (0.2%) would be safer for paediatric patients, but their efficacy is unknown.
- Addition of dexmedetomidine to reduced dose ropivacaine 0.2% provided increased safety margin without compromising the analgesic efficacy in paediatric TAP block.

Patients were taken inside the operation theatre, standard monitors were applied, and premedication with midazolam 0.05 mg kg^{-1}, fentanyl 2 μg kg^{-1} and atropine 0.02 mg kg^{-1} intravenously was done. Baseline heart rate (HR) and mean arterial pressure (MAP) were recorded followed by 3 minutes of pre-oxygenation. Induction of anaesthesia was done with sevoflurane 6-8%, and relaxation was achieved with intravenous atracurium 0.5 mg kg^{-1}. Patients were intubated orally using an appropriate size endotracheal tube. Anaesthesia was maintained with a mixture of oxygen, nitrous oxide and sevoflurane targeting 1.3 × MAC, while paralysis was maintained with atracurium.

Under aseptic precautions, TAP block was performed unilaterally on operative side, using 5–10 MHz, high frequency, linear probe in "Triangle of Petit" (posterior approach). External oblique, internal oblique and transverse abdominis muscles were identified at the level of midaxillary line between the 12th rib and the iliac crest, and the block was performed using a 23-gauge spinal needle, in-plane technique. After negative aspiration of blood, drug was injected as per group allocation and was considered failure in the absence of echolucent biconvex shape space between the two muscles. Failures were included in analysis on intention-to-treat basis.

Hemodynamic data just after the premedication was considered as baseline. If the heart rate, MAP or both increased by 15% relative to the baseline after the skin incision or during the course of surgery, 0.5 μg kg^{-1} of fentanyl was administered which was recorded. The heart rate and MAP were recorded every 15 minutes during the surgery. Pain was assessed by an independent anaesthetist using Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) at 10, 30, 60 minutes post-operatively and hourly up to 6 hours and then every 6 hours up to 24 hours. If the pain score was >6, paracetamol was given as the rescue analgesic at a dose of 10 mg kg^{-1} intravenously (up to 60 mg kg^{-1} day^{-1}).

Mean time to first rescue analgesic within 24-hour time frame was considered as primary objective for the purpose of sample size calculation. Secondary objectives were total

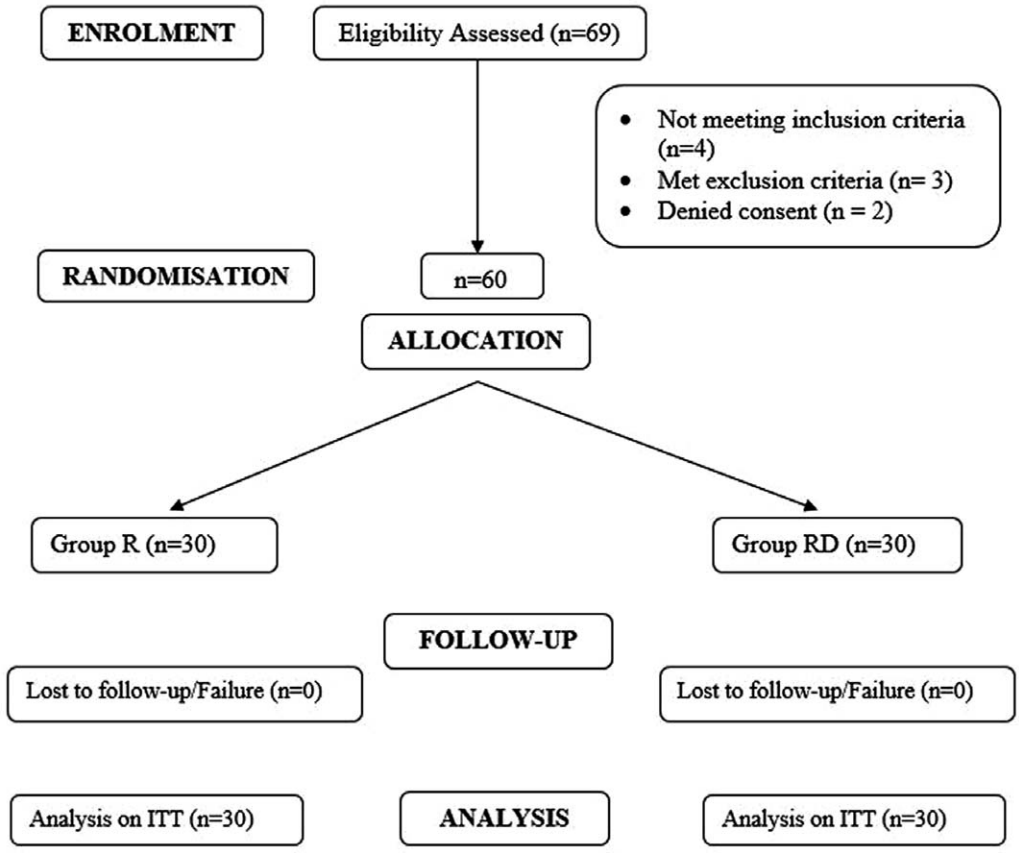

Figure 1. CONSORT diagram showing randomisation, allocation, and analysis of study participants
n: number of patients
R: ropivacaine
RD: ropivacaine–dexmedetomidine
ITT: intention to treat analysis

analgesic consumption in 24 hours, number of patients requiring rescue analgesia, post-operative pain score using CHEOPS, Ramsay sedation scores, hemodynamic parameters, i.e., HR and MAP, and any adverse events, such as nausea and vomiting. The pain scores were noted by anaesthesiologist not aware of the study groups, and patient was discharged as per Pediatric Post-anaesthesia Discharge Scoring System (PED-PADSS) criteria.

Statistical Analysis

Sample size was calculated with the hypothesis that analgesia provided by combination of 1 μg kg^{-1} of dexmedetomidine to 0.2% ropivacaine is inferior to 0.375% ropivacaine alone by more than the non-inferiority margin (–Δ) of 30% (preserved fraction 70%). The limit of non-inferiority was set on the basis of extrapolation of data from a previous meta-analysis[6] that showed around 30% decrease in analgesic requirements with the use of TAP block. On the basis of initial pilot study mean time to first rescue analgesia with ropivacaine was 9.3 ± 3.5 hours (d = 9.3-6.5, where "d" the largest acceptable difference). Using type I error $\alpha = 0.05$, and type II error $\beta = 0.2$, it was required to include 26 patients per group (PS Power and Sample Size Calculator version 3.0.43; Dupont WD, Plummer, WD). Considering 5% drop-out, it was decided to include 30 patients per group. Statistical analysis was performed using Graph Pad Prism 5.00 (Graph Pad Software, San Diego, CA, USA). Results are presented in number, mean and SD or frequencies (%), as appropriate. Continuous data were compared using unpaired student's t-test, categorical using Chi-square test. Kaplan–Meier curve with log rank test and Cox proportional hazard ratio for rescue analgesic requirement was performed. P of $<.05$ was considered statistically significant.

Results

Patient characteristics with respect to age, weight, sex, and duration of surgery remained similar in both the study group (Table 1). Mean time to first rescue analgesia was 10.82 ± 2.16 hours in group R and 16.32 ± 3.11 hours in group RD

Table 1. Patient Characteristics

Parameters	Group R (n = 30)	Group RD (n = 30)	*P*
Age (years)	4.86 ± 2.04	4.83 ± 2.00	.9543
Weight (kg)	14.93 ± 2.50	14.43 ± 2.77	.4659
Sex (male/female)	24/6	22/8	.2778
Duration of surgery (minutes)	33.13 ± 4.02	32.56 ± 3.16	.5439

n, number of patients; data expressed as mean ± SD; $P \leq .05$ is considered significant; R, ropivacaine; RD, ropivacaine–dexmedetomidine.

Table 2. Analgesia Characteristics

Characteristics	Group R	Group RD	*P* or 95% CI
Mean pain free time in hours (time to first rescue analgesic)	10.82 ± 2.16	16.32 ± 3.11	<.0001
Median pain free time in hours (time to first rescue analgesic)	10.50	17.00	–
Hazard ratio of pain	4.011	0.24	8.0-28.4 (R) 0.03-0.12 (RD)
Number of patients requiring analgesic in 24 hours (n)	30	22	.0046
Mean analgesic requirement in Ist 24 hours (mg kg^{-1} day^{-1})	48.3 ± 7.8	23.6 ± 8.4	.0001

n, number of patients; data expressed as mean ± SD or median; $P \leq .05$ is considered significant; R, ropivacaine; RD, ropivacaine–dexmedetomidine.

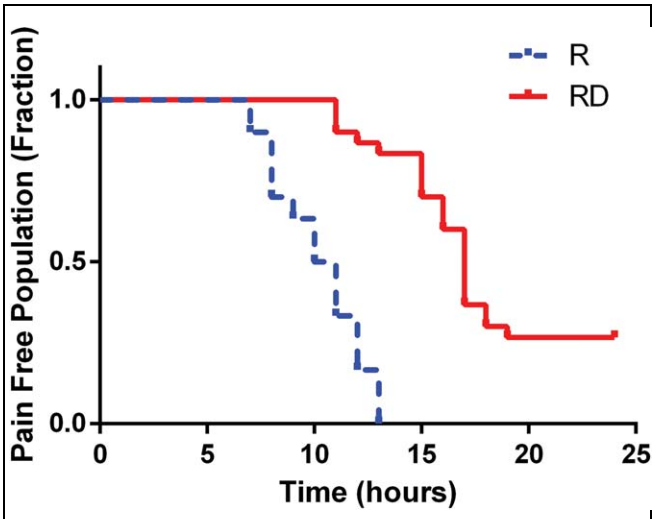

Figure 2. Kaplan–Meier survival plot showing increased pain free period in group RD
R: ropivacaine
RD: ropivacaine–dexmedetomidine

($P < .001$). Kaplan–Meier survival analysis followed by Log rank (Mantel–Cox) test was performed for pain free period (time to first analgesic requirement) that showed significantly improved pain control in group RD ($P < .0001$) (Table 2 and Figure 2). Median pain free time in groups R and RD was 10.5 and 17.0 hours, respectively (95% CI: 0.3724–1.025). Cox proportional hazard ratio for rescue analgesic requirement in group R to RD was 4.0 (95% CI of ratio: 8.012–28.42). All patients of group R while 22 patients of group RD required rescue analgesia in Ist 24 hours ($P = .0046$). Mean consumption of analgesic requirement (mg kg^{-1} day^{-1}) in Ist 24 hours was 48.3 ± 7.8 and 23.6 ± 8.4 ($P = .0001$) in group R and RD, respectively (Table 2). Comparison of the intergroup post-op CHEOPS scores at various intervals showed significant difference from 2 hours onwards that continued till 24 hours post-op with lower scores in group RD. Mean CHEOPS score was 6.30 ± 1.74 in group R while 4.84 ± 1.1 in group RD ($P = .02$) but during initial post-operative period of 4 hours it was comparable in both the groups. Median CHEOPS scores were 6.11 and 4.45 in group R and RD, respectively (Table 3). Post-op sedation was evaluated using Ramsay sedation score and was found to be significantly greater in group RD 3 hours onwards post-operatively ($P < .05$). The mean sedation score was >2 at all times in the patients of group RD during the post-operative period (Table 4). There was a statistically significant decrease in heart rate from 30 minutes onwards in group RD (129.6 ± 6.3, 121.6 ± 6.9, 114.2 ± 6.2, 99.8 ± 6.9, 95.9 ± 6.2, 92.3 ± 5.2 per minute) compared to group R (130.4 ± 6.4, 123.8 ± 6.7, 116.6 ± 6.1, 106.4 ± 6.4, 102.4 ± 6.2, 100.6 ± 5.9 per minute) measured at time baseline, 0, 15, 30, 45, 60 minutes, respectively (Figure 3). Bradycardia was not noted in any of the patients and none of the patients required any intervention for the same. Intergroup

Table 3. Post-operative CHEOPS score

Variable Time	CHEOPS pain score		*P*
	Group R	Group RD	
0.0 hour	4.16 ± 0.87	4.13 ± 0.90	.89
0.5 hour	4.2 ± 0.90	4.20 ± 0.86	1.00
1.0 hour	4.33 ± 1.10	4.22 ± 1.55	.75
2.0 hours	5.56 ± 0.95	4.24 ± 1.10	.001
3.0 hours	5.78 ± 1.30	4.34 ± 1.70	.0005
4.0 hours	5.89 ± 0.85	4.42 ± 1.64	<.001
5.0 hours	6.33 ± 0.90	4.49 ± 1.57	<.001
6.0 hours	6.81 ± 0.90	4.57 ± 1.51	<.001
9.0 hours	6.97 ± 1.10	4.63 ± 1.71	<.001
12 hours	7.42 ± 1.20	4.78 ± 1.58	<.001
18 hours	8.21 ± 1.50	6.45 ± 1.47	<.001
24 hours	10.02 ± 1.80	7.74 ± 1.20	<.001
Mean CHEOPS score	6.3 ± 1.74	4.84 ± 1.1	.024
Median CHEOPS score	6.11	4.45	

h, hour; data expressed as mean ± SD or median; $P \leq .05$ is considered significant; R, ropivacaine; RD, ropivacaine–dexmedetomidine; CHEOPS, Children's Hospital of Eastern Ontario Pain Scale.

Table 4. Post-operative Ramsay Sedation Score

Sedation score	Group R	Group RD	*P* value
15 minutes	1.42 ± 0.46	2.54 ± 0.51	<.001
30 minutes	1.47 ± 0.49	2.59 ± 0.53	<.001
45 minutes	1.56 ± 0.57	2.43 ± 0.49	<.001
60 minutes	1.87 ± 0.42	2.61 ± 0.59	<.001
2 hours	1.46 ± 0.51	2.27 ± 0.47	<.001
3 hours	1.71 ± 0.43	2.19 ± 0.42	<.001

Data expressed as mean ± SD; $P \leq .05$ is considered significant; R, ropivacaine; RD, ropivacaine–dexmedetomidine.

analysis did not show any significant difference in MAP throughout the intraoperative period. Group R has MAP of 73.9 ± 5.8, 70.4 ± 5.7, 72.6 ± 5.8, 75.6 ± 6.1, 76.0 ± 6.4, 74.8 ± 7.2 mmHg, while group RD has 73.2 ± 6.9, 72.0 ± 4.4, 72.9 ± 5.3, 73.4 ± 6.7, 72.9 ± 6.7, 71.8 ± 7.7 mmHg measured at time baseline, 0, 15, 30, 45, 60 minutes, respectively. No statistically significant difference was observed at any time (Figure 4). There was no incidence of hypotension requiring intervention in any of the patients. No significant adverse effects in the form of hypotension, bradycardia or respiratory depression were noted except nausea and vomiting in two patients of group R and one of group RD.

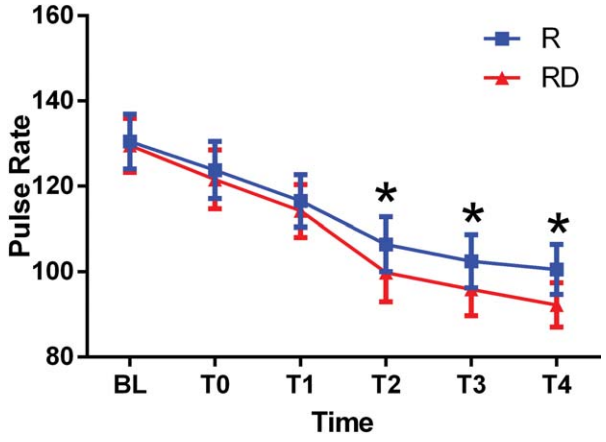

Figure 3. Shows variation of pulse rate with time in group R and RD
R: ropivacaine
RD: ropivacaine–dexmedetomidine
BL, T0, T1, T2, T3, T4: baseline, 0, 15, 30, 45, 60 minutes, respectively
values with "*" are significant

Discussion

We hypothesised that analgesia provided by combination of 1 μg kg^{-1} of dexmedetomidine to 0.2% ropivacaine is inferior to 0.375% ropivacaine alone in USG guided paediatric TAP block. The results of the present study revealed that

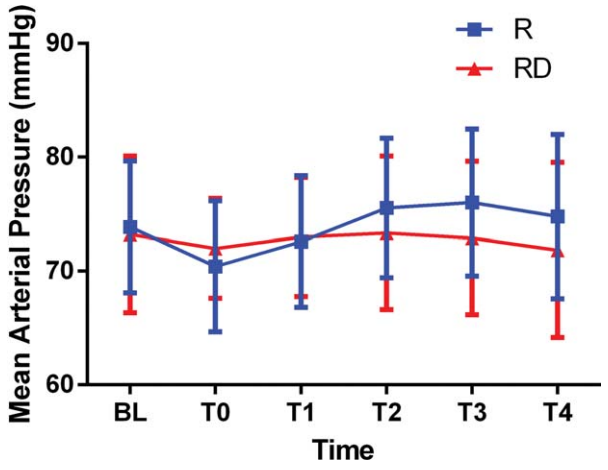

Figure 4. Shows variation of MAP with time in group R and RD
R: ropivacaine
RD: ropivacaine–dexmedetomidine
BL, T0, T1, T2, T3, T4: baseline, 0, 15, 30, 45, 60 minutes, respectively
values with "*" are significant

combination of dexmedetomidine with reduced concentration of ropivacaine (0.2%) produced significantly longer duration of post-operative analgesia and lowered post-operative CHEOPS pain score compared to 0.375% ropivacaine.

Various regional techniques, such as TAP block, quadratus lumborum, rectus sheath, transversalis fascia plane, ilioinguinal and iliohypogastric nerve blocks, are being used in routine practice for post-operative analgesia in abdominal surgeries. The TAP block has shown to provide promising results in terms of effective intra-operative and post-operative analgesia in adults following lower abdominal surgery.[7,8] It blocks the nerve roots to the anterior abdominal wall and facilitates effective post-operative pain control; however, it does not provide surgical analgesia. Evidence-based literature shows that combined regional and general anaesthesia provide better postop pain control, reduce opioid requirements, decrease hospital stay and improve outcomes in paediatric patients.[9–12] A large multicentric safety analysis evaluated the incidence of overall and specific complications resulting from the performance of the TAP block in children. It was concluded that the overall incidence of complications associated with the TAP block in children was quite low, and safety concerns should not be a major barrier in children as long as appropriate local anaesthetic dose regimens are selected.[13] The use of USG guidance in TAP block has further improved the safety and reliability of the block. It allows the real time visualisation of the needle, muscle layers, the peritoneum and intraperitoneal visceral structures along with precise drug deposition in the fascial plane.

TAP block is usually performed with large volume of LA which might result in systemic toxicity if higher concentrations are used in paediatric patients where margin of safety is narrow. Hence, addition of adjuvants such as dexmedetomidine to LA seems a feasible option in TAP block which helps in prolonging the time to first rescue analgesia, reduces post-operative pain scores and enhances patient satisfaction albeit with an increase in adverse effects.[14–16]

In the present study, it was observed that addition of dexmedetomidine to lower concentration of ropivacaine significantly extended the time to first recue analgesic along with reduction in post-op pain scores. Xiao et al.[17] in their study on adult patients undergoing abdominal hysterectomy demonstrated a similar prolongation in time to first rescue analgesic by 15 hours with addition of 0.5 μg kg^{-1} dexmedetomidine to 0.25% levobupivacaine. Similarly, various studies in adults have shown that dexmedetomidine reduced the amount of anaesthetics and improved post-operative analgesia when used as an adjuvant to LA in TAP block.[18–21] Although there is paucity of literature regarding the use of dexmedetomidine in paediatric TAP block, we could find the study by Raof et al.[22] who conducted a randomised, double-blind, up-down, dose-finding study in hernia repair and concluded that addition of 2 μg kg^{-1} of dexmedetomidine to 0.125% bupivacaine significantly reduced the Minimum Local Anaesthetic Concentration of bupivacaine and reduced the analgesic requirement.

The results of this study indicate that post-operative mean CHEOPS score was significantly lower in dexmedetomidine group compared to ropivacaine alone. In addition, the total analgesic dosage required within 24 hours post-operatively was greater with the standard ropivacaine. This is in agreement with the findings of previous study[22] who demonstrated that addition of dexmedetomidine reduced the pain scores and post-operative analgesic requirement.

This study showed that significantly higher sedation scores were noted for up to 3 hours post-operatively in dexmedetomidine group compared to ropivacaine alone which is consistent with studies investigating the use of dexmedetomidine in paediatric peripheral nerve blocks.[22–24]

With regard to hemodynamic parameters, there was a decreasing trend in the HR compared to baseline in both the groups. Although greater reduction was observed with the use of dexmedetomidine, it did not reach the limits of significance. Similar stable hemodynamic profile of dexmedetomidine has also been published in other studies.[14,22] Further, no significant adverse events were noted with the use of dexmedetomidine in the form of hypotension, bradycardia or respiratory depression except nausea and vomiting in one patients.

Although this was a randomised study, there are a few limitation in our study which should be taken into account while extrapolating the results to external population. First, it was a

single centred study where sample size was calculated on basis of extrapolation of data due to lack of literature in similar settings. Study might be under-powered if there is any discrepancy in setting the inferiority margin. Second, superiority was concluded on the basis of a non-inferiority trial, although this is not wrong, but multicentric, larger, superiority trials must have given a more holistic view. Finally, we in our study did not assess the effect of dexmedetomidine on hospital discharge time that has implications in daycare surgeries.

Conclusion

In conclusion, combination of 1 μg kg^{-1} dexmedetomidine with reduced concentration of ropivacaine (0.2%) produced significantly longer duration of post-operative analgesia and lowered post-operative CHEOPS pain score in comparison with 0.375% ropivacaine alone in USG guided TAP block for paediatric hernia repair.

Ethics Committee Approval: Ethics committee approval was received from the Institutional Ethics Committee, J.N. Medical College (Approval No.-71/FM/IEC/2019).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.N., M.A.; Design - F.N., M.A.; Supervision - F.N., M.A.; Resources - F.N., M.A.; Materials - F.N., M.A., A.K., D.S.M.; Data Collection and/or processing - A.K., D.S.M.; Analysis and/or Interpretation - F.N., M.A., A.K., D.S.M.; Literature Search - F.N., M.A., A.K., D.S.M.; Writing Manuscript - F.N., M.A., A.K., D.S.M.; Critical Review - F.N., M.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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