

Efficacy and Safety of Dexmedetomidine Combined with Bupivacaine in Infants' Surgeries: A Randomized Controlled Trial

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Abstract

Background: Dexmedetomidine has been identified as a good sedative agent in adult patients. It is usually added to local anesthetic in spinal anesthesia (SA). However, its use as an adjuvant in infant surgeries has not been well studied due to the scarcity of data. **Aim:** In this study, we aim to investigate the efficacy and safety of dexmedetomidine combined with bupivacaine in SA. **Materials and Methods:** in this randomized clinical trial, we included 46 infants who underwent infra-umbilical surgeries. We allocated patients into two groups: group 1 received bupivacaine only, and group 2 received 0.3µg/kg dexmedetomidine in addition to bupivacaine 0.5%. We assessed efficacy through evaluation of the onset and duration of sensory and motor block and time to discharge from the post-anesthesia care unit (PACU), while safety was assessed through monitoring of hemodynamics and rate of complications. **Results:** we found that using 0.3µg/kg dexmedetomidine in addition to bupivacaine 0.5% (group 2) was associated with a significantly prolonged duration of sensory and motor block compared to group 1. Time to discharge from PACU was earlier with group 2, but not significantly different from group 1. Although Group 1 did not witness any complications; group 2 had limited side effects that were managed appropriately. **Conclusions:** the combination of 0.3µg/kg dexmedetomidine with bupivacaine is safe and efficient in the anesthesia of infants undergoing minor surgeries.

Keywords: infra umbilical surgeries; Dexmedetomidine; Bupivacaine; Infants; spinal anesthesia.

Introduction

The aim of anesthesia in pediatric patients is to provide good operating conditions for the surgeon while minimizing any harmful

psychological and physiological consequences for the patients⁽¹⁾. Both parents as well as pediatric anesthesiologists are very aware that anesthetizing infants is much more difficult than anesthetizing older chil-

dren and young adults. Peak parental anxiety about anesthesia and surgery occurs when their child's age is below one year, and surgical mortality rates support this parental anxiety⁽²⁾. The use of regional anesthesia in neonates and infants may be beneficial in many clinical scenarios. These include the avoidance of airway manipulation or respiratory depression, and a desire to improve intraoperative pain management or to decrease the potential neurotoxic effects of intravenous or inhaled general anesthesia⁽³⁾. Dexmedetomidine, a central alpha-2 agonist, has been approved by the United States Food and Drug Administration (USFDA) as a sedative in intensive care units (ICU) and for short procedures. Its popularity as a short-lived sedative is because, although it does produce sedation, it does not cause respiratory depression, unlike other sedatives such as opioid⁽⁴⁾. Dexmedetomidine has been used as an adjuvant to different LAs in adults resulting in improving the quality and duration of sensory and motor blockade. Additionally it decreases the used dose of local anesthetic⁽⁵⁾. Dexmedetomidine is often combined with bupivacaine during spinal anesthesia. It has been found to have several beneficial properties such as: reduction of the need for analgesia and several postoperative side effects⁽⁶⁾. Several studies have examined the role of dexmedetomidine as a sedative in adult patients, but not in infants^(7,8). Therefore, we aim to evaluate the efficacy and safety of combining dexmedetomidine with bupivacaine in infants' surgeries.

Patients and Methods

In this randomized controlled study, we included 46 infants who underwent infra-umbilical surgeries at operating theatres at

Suez Canal University Hospitals. Twenty-three patients were randomly assigned to the control group and received SA with bupivacaine 0.5% only, and the other 23 infants received Dexmedetomidine 0.3µg/kg as an adjuvant to bupivacaine 0.5%. After gaining informed consent from parents, infants underwent a thorough medical and perinatal history, general and local examination, and routine laboratory tests. Preoperative measures were conducted as follows: Baseline hemodynamics parameters: (heart rate, mean arterial blood pressure, respiratory rate, oxygen saturation, and temperature) were recorded. Intraoperative measures included monitoring of the patients done through GE (General Electric) healthcare CARESCAPE B450 monitor including pulse oximeter, ECG, temperature probe (axillary), and non-invasive blood pressure have been done. All general anesthesia equipment and resuscitative drugs were prepared and establishment of intravenous line by 24G cannula had been done. A standardized intraoperative fluid therapy had been given to all patients in dose of 6 ml/kg/h of lactated ringer and glucose 5% in ratio 4:1 by using syringe pump to control the rate of infusion. Oxygen was given through nasal cannula at a rate of 2 L/min. All patients were pre-medicated 30 minutes before the procedure with: 1) Midazolam 0.5 mg/kg orally by syringe. 2) Atropine 0.02 mg/kg IM. 3) EMLA™ cream, 0.5-1ml applied to the lumbar and sacral region. Infants were positioned in lateral position with head extension and hip flexion. Complete aseptic measures were followed: hands disinfection by alcohol, sterile gloves were used, careful disinfection of the patients back with betadine solution, and sterile towel applied on the patients' back. Lumbar puncture was

done in one of these levels: L4-L5 or L5-S1. Then, patients were put in a supine position with head elevation immediately after injection till the level had been stabilized. We assessed the level of sensory block by attempting to elicit a grimace to bilateral firm skin pinch at each dermatome every 2 minutes. And motor block was assessed by observation of the lower limb movement using a modified Bromage scale. The operation was allowed to begin after both lower limbs became flaccid. Successful spinal block was recognized by loss of lower limb movement with normal tone in both arms and these patients had not reacted to noxious stimulation with sustained crying and easily comforted by giving them a 10% glucose solution by pacifier. The technique was considered failed in the following situations: Zero or one on the Bromage scale after 10 minutes; inability to obtain freely flowing CSF after three trials or the infant was given GA if the technique was considered failed then added to the withdrawal group and did not count in the study. We monitored the patients for any complications and managed them accordingly. *Bradycardia*: Heart rate <100 beats/min or $>20\%$ decrease in baseline heart rate, which is treated by atropine in a dose of 0.01-0.02 mg/kg IV. *Hypotension*: MAP of <35 mm Hg or $>30\%$ decrease in MAP from baseline, which was treated by IV fluids, if it was not enough then ephedrine in a dose of 0.1-0.2 mg/kg IV was given. *Oxygen Desaturation*: decrease in $SpO_2 < 90\%$ that was associated with bradycardia, which was treated by oxygen nasal cannula 2 L/min. *Apnea*: A pause in breathing lasting more than 15 sec, or a pause in breathing of any duration leading to $SpO_2 < 80\%$ or bradycardia, which treated by oxygen face mask ventilation was done.

Statistical Analysis

The statistical analysis was performed using a Statistical Package for the Social Sciences SPSS® version 25 (IBM corporation, Armonk, NY, USA) for Windows operating system. Descriptive data was expressed as mean and SD for continuous variables, and count and/or percentages (%) for dichotomous variables. Unless stated otherwise, results are mean \pm SD. T-test was used to analyze continuous variables between the study groups, while discrete (categorical) variables were analyzed using the Chi-square. The level of statistical significance was $p < 0.05$. Presentation of the statistical outcomes in the form of tables and graphs was performed using the "Microsoft Office Excel® 365" program.

Results

In this study, 46 patients were included who underwent elective minor infra-umbilical surgeries. Twenty-three patients in (group 1) received spinal anesthesia with bupivacaine 0.5% only, 23 patients in (group 2) received dexmedetomidine 0.3 μ g/kg as an adjuvant to bupivacaine 0.5%. Table 1 demonstrates the demographic data of patients, including age and sex. The patients' age distribution was around 6 months. The number of males was higher than females. There was no statistically significant difference between the two groups ($p > 0.05$). Table 2 expresses the maximum sensory level, the onset of sensory and motor block, the duration of sensory and motor block, and the time to discharge from PACU. Among thoracic sensory levels, T6 was the most commonly perceived among groups 2 and 4, while T7 was the most common one among groups 1 and 3. T8 was the least

sensed level. The onset of sensory block was around longer, while the onset of motor block was shorter minutes in group 2. However, there is no statistically significant difference. The duration of sensory and motor block was significantly different between the studied groups with the least duration witnessed in group 1. Where time to discharge was assessed there was no statistically significant difference between the two groups. Graph 1 shows the changes in heart rate mean values and SD at different time intervals between the study groups. Patients from group 1 had the lowest heart rate during the whole period of monitoring. There was no statistically significant difference in heart rate between the studied groups. Regarding blood pressure, group 1 recorded the lowest mean blood pressure during the period between pre-induction till 5 minutes, and around 15 minutes postoperative. While on the other hand, group 2 recorded the lowest mean blood pressure during the period between 30 minutes postoperative up to 90 minutes. There was no statistically significant difference in mean arterial blood pressure between the studied groups (Graph 2). Regarding the respiratory rate, group 1 recorded the lowest respiratory rate during the period between pre-induction till 5 minutes postoperative, and the period between 45 minutes postoperative up to 90 minutes. While

Discussion

One of the limitations of bupivacaine alone in SA is that it provides a block that is of shorter duration in infants and children. Therefore, to prolong the duration of SA, several adjuvants such as epinephrine, ne-

Group 2 recorded the highest respiratory rate during the same period mentioned earlier. There was no statistically significant difference in respiratory rate between the studied groups (Graph 3). Graph 4 shows oxygen saturation, it was within normal ranges during the whole monitoring period. There was no statistically significant difference in oxygen saturation between the studied groups. Table 3 expresses the rate of complications among the study groups which were mainly due to an increase of vagal tone. Group 1 did not witness any complications. Bradycardia was the most frequent complication that occurred in 3 patients in group 2, followed by oxygen desaturation that occurred was hypotension with 2 patients only. Hypotension and apnea presented in only 1 patient. There were no cases who experienced hematoma at the site of injection, high spinal block, nausea, vomiting, or delay of breast feeding. All complications that occurred were managed successfully and the cause was reversible.

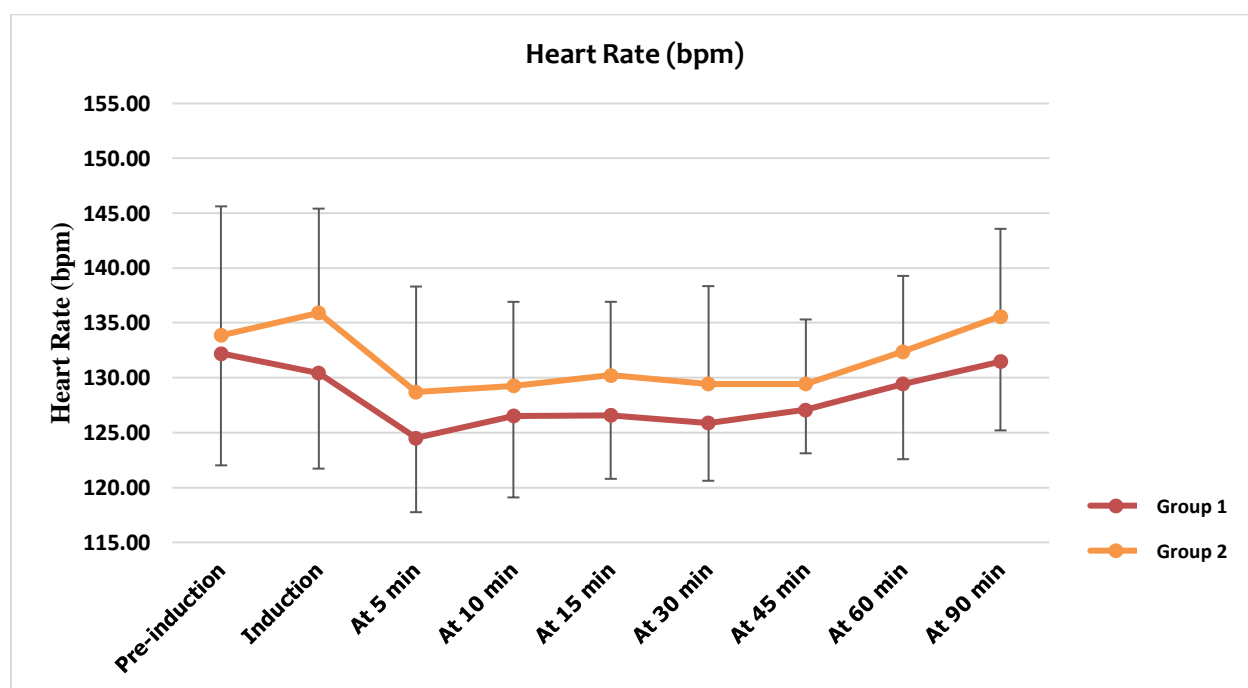
Table 1: Characteristics of patients.

		Group 1 (n = 23)	Group 2 (n = 23)	P value
Age (months)		5.74 ± 2.6	6.17 ± 2.75	0.435
Sex	Male	13 (56.5%)	14 (60.9%)	0.950
	Female	10 (43.5%)	9 (39.1%)	

Data are presented as mean ± SD and frequency (%)

ostigmine, clonidine, morphine, fentanyl, and dexmedetomidine are added to bupivacaine⁽⁹⁾. So our study was conducted to determine the safety and efficacy of dexmedetomidine as an adjuvant to intrathecal hyperbaric bupivacaine in infants undergoing infra-umbilical surgeries at Suez Canal University Hospitals.

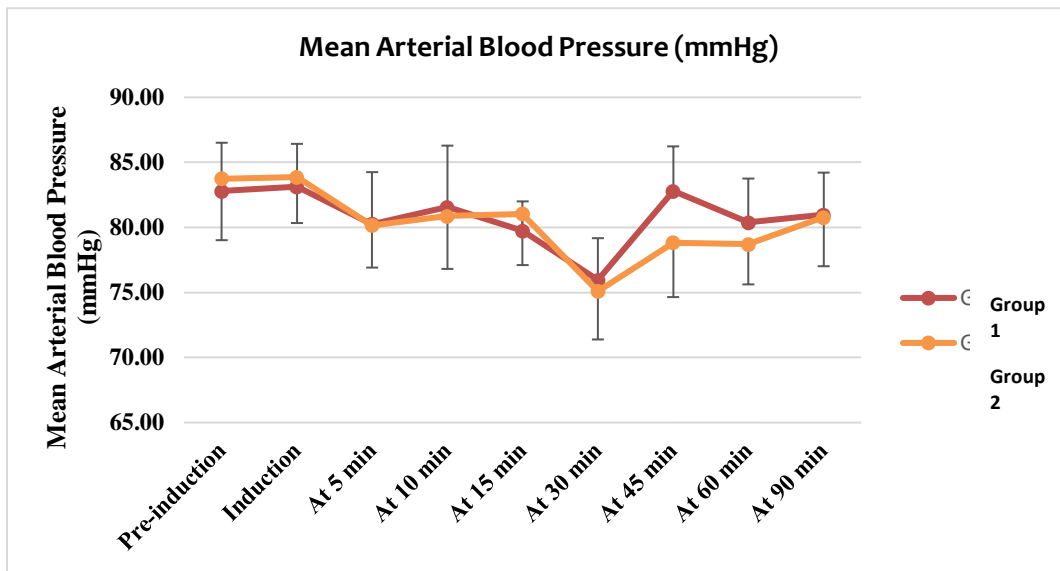
Table 2: level of spinal blockade, onset and duration of sensory and motor block.				
		Group 1 (n=23)	Group 2 (n=23)	P value
Sensory level blockade	T6	9 (39.1%)	9 (39.1%)	0.146
	T7	10 (43.5%)	14 (60.9%)	
	T8	4 (17.4%)	0 (0)	
Onset of sensory blockade (min)		2.96 ± 1.065	2.61 ± 0.722	0.548
Onset of motor blockade (min)		3.00 ± 0.953	3.52 ± 0.994	0.229
Duration of sensory blockade (min)		64.78 ± 9.229	123.48 ± 7.751	0.000*
Duration of motor blockade (min)		43.26 ± 2.435	99.35 ± 6.958	0.000*
Time to discharge from PACU (min)		13.91 ± 3.679	15.21 ± 3.190	0.093



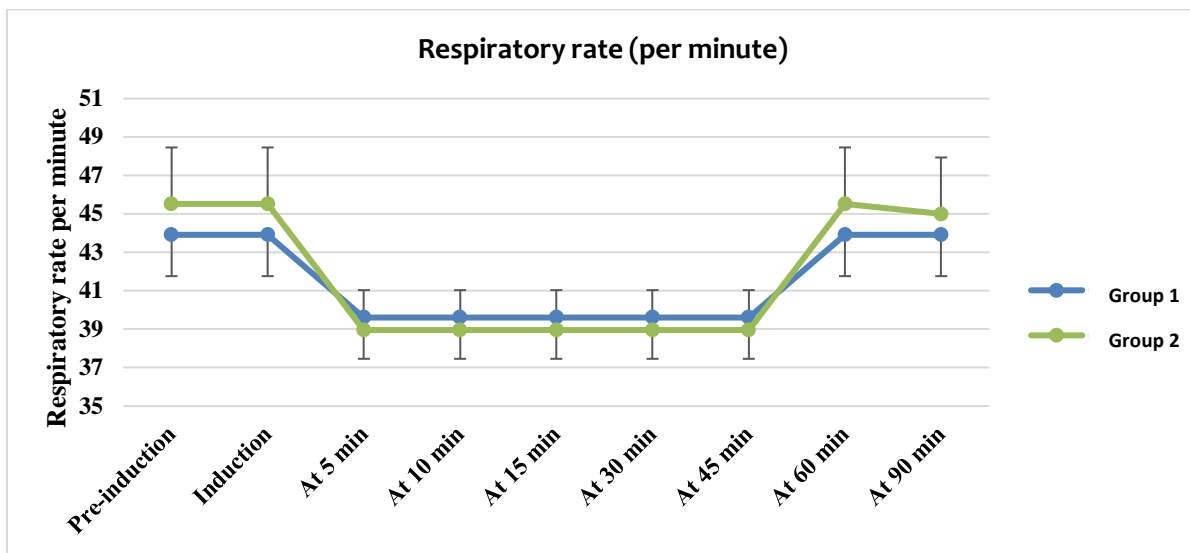
Graph 1: Heart rate changes at different time intervals.

Efficacy was assessed by measuring the onset and duration of sensory and motor block and time to discharge from PACU, while safety was assessed by monitoring the hemodynamics, in addition to the possible complications that might have occurred. The study included 46 patients allocated into 2 groups; one control group received only intrathecal hyperbaric bupivacaine 0.5% while the other group received

0.3 µg/kg intrathecal dex-medetomidine as an adjuvant to hyperbaric bupivacaine 0.5%. We found that adding dexmedetomidine to bupivacaine achieved better results regarding efficacy and was associated with minimal side effects that could be tackled. Previous studies augmented our findings. Tang et al concluded that 5 µg intrathecal dexmedetomidine reduced the ED₅₀ of spinal hyperbaric ropivacaine during cesarean section by approximately 18%.



Graph 2: Mean Arterial Blood Pressure changes at different time intervals.



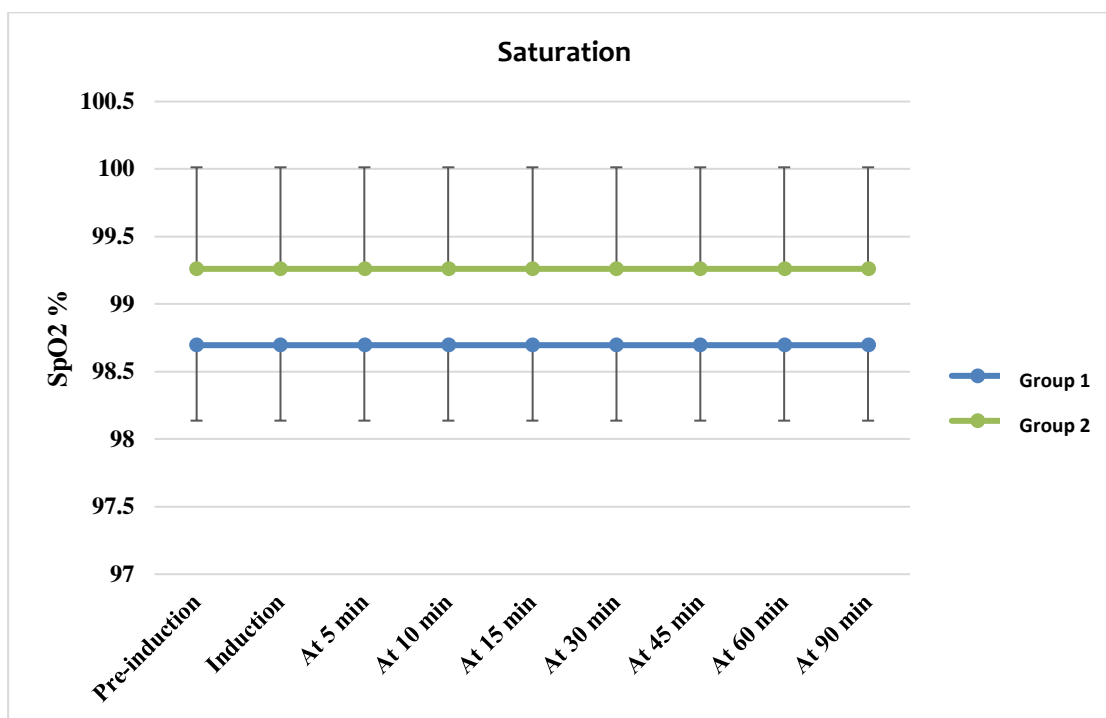
Graph 3: Respiratory rate changes at different time intervals.

Also, Liu 2019 found that 5 µg intrathecal dexmedetomidine enhances the efficacy of spinal bupivacaine by 24% in patients undergoing cesarean section with SA. No additional side effect was observed by adding spinal dexmedetomidine^(10,11). In our study the sensory level blockade and the onset of sensory and motor blocks were not statistically significant different between the studied groups. However, the duration of sen-

sory and motor block had a statistically significant difference between the studied groups, with group 2 was significantly higher. Comparison of the results in the current work with similar studies on young populations was not possible due to the lack of resources that support intrathecal dexmedetomidine in infra-umbilical surgeries in infants. However, several studies are available in adults. Similar to our results, Singh

et al. conducted a prospective, comparative, randomized study involving 60 adult

patients with ASA classes I and II undergoing infraumbilical surgery on SA



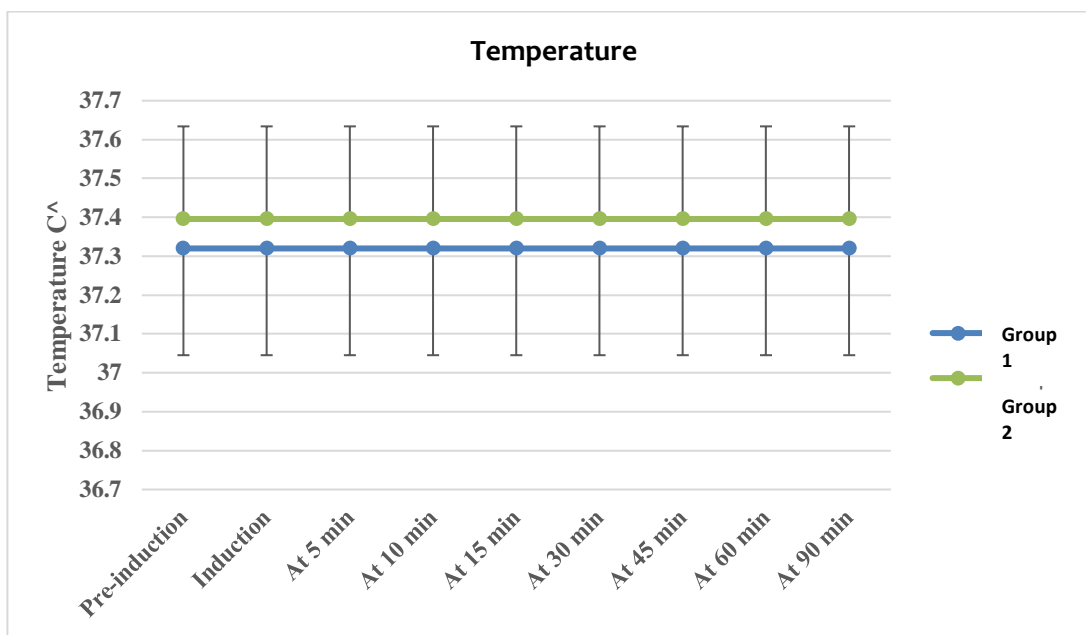
Graph 4: Oxygen saturation percentage at different time intervals.

The patients were divided into three groups. Each group received 4 or 8 g dexmedetomidine with 3 ml bupivacaine, with no statistically significant difference in the onset of sensory and motor blockade, while the duration of sensory and motor blockade was significantly prolonged with increasing dexmedetomidine doses⁽¹²⁾. In a recent study by Saha et al 105 adult patients who underwent infra umbilical surgery in the context of SA were divided into three equal groups. Each group received intrathecally 5, 7.5, and 10 g dexmedetomidine in addition to 15 mg bupivacaine. They found a statistically significant and dose-dependent reduction in the meantime to the peak of sensory block (3.9, 3.3, and 2.9 minutes; $P=0.001$) and the peak of motor block (5.6, 5.3 and 4.8 minutes; $P=0.001$)⁽¹³⁾. Shen et al claimed that

the use of intrathecal dexmedetomidine during Cesarean section may shorten the onset time of SA and increase the duration of sensory and motor block⁽¹⁴⁾. In addition, Gupta et al showed that intrathecal 0.5% bupivacaine 3 ml in combination with 2.5 g, 5 g, or 10 g dexmedetomidine was safe and did not increase the incidence of side effects. Furthermore, the addition of 10 g compared to 2.5g or 5g of intrathecal dexmedetomidine to 0.5% hyperbaric bupivacaine was associated with a significantly earlier onset of sensory and motor block and a longer duration of sensory and motor block⁽¹⁵⁾. In contrast to our study, Zhang et al, in a recent prospective, randomized, double-blind, placebo-controlled study, evaluated 120 ASA I and II patients undergoing elective cesarean delivery under SA. Pa-

tients were randomized into four groups to be treated with intrathecal ropivacaine 12 mg alone or in combination with dexmedetomidine 5 g, 7.5 g, and 10 g. There was no statistically significant onset of sensory and motor block in all four groups, while dexmedetomidine prolonged the duration of sensory and motor block compared to the control group⁽¹⁶⁾. To our surprise, the

time to discharge from PACU was not statistically significantly different between the studied groups. Handlogten et al results had a different opinion where SA using dexmedetomidine had a role in decreasing the time to discharge from PACU to a median of 49 minutes, which is shorter in comparison to the patients who received other drugs or had GA⁽¹⁷⁾.



Graph 5: Temperature changes at different time intervals.

Table 3: Possible complications that might have been occurred.			
Complications	Group 1 (n=23)	Group 2 (n=23)	P value
Bradycardia	0 (0)	3 (13%)	0.140
Oxygen Desaturation	0 (0)	2 (8.7%)	0.507
Hypotension	0 (0)	1 (4.3%)	0.563
Apnea	0 (0)	1 (4.3%)	0.563
Hematoma at the site of injection	0 (0)	0 (0)	-
High spinal block	0 (0)	0 (0)	-
Nausea & vomiting	0 (0)	0 (0)	-
Delay of breast feeding	0 (0)	0 (0)	-

This is longer than in the present study, but this can be attributed to different routes of dexmedetomidine where nasal dexme-

detomidine was used in Handlogten’s study, while in our study, intrathecal dexmedetomidine was used. In addition, dex-

medetomidine was added to bupivacaine which augmented its efficacy. Other important findings in our study were the hemodynamics (heart rate, mean arterial blood pressure, respiratory rate, oxygen saturation, and temperature) throughout the study period. There were no statistically significant differences in these variables between the 2 studied groups. Interestingly, hemodynamic effects of SA including hypotension and bradycardia, are uncommon in neonates and infants despite the high levels of blockade required. This is likely due to smaller venous capacitance in the lower limbs leading to less pooling and to the immature sympathetic nervous system resulting in less dependence on vasomotor tone to maintain blood pressure⁽¹⁸⁾. In line with our findings, Gupta et al showed that intrathecal 0.5% bupivacaine 3 ml combined with 2.5 µg, 5 µg, or 10 µg dexmedetomidine was safe and did not increase the incidence of adverse effects⁽¹⁵⁾. In contrast to our findings in Fares et al study, the intraoperative hemodynamic changes only decreased in the dexmedetomidine group, in contrast to the fentanyl and control groups. This might be due to the difference in the types of patients and surgical procedures minor and medium surgical procedures in our study versus pediatric patients with major abdominal surgical procedures, with progressively fragile patients and more noteworthy fluid shifts expected in which may have resulted in hemodynamic changes⁽¹⁹⁾. However, in Mahendru et al found no statistically significant difference in MAP and heart rate within the studied groups (which included fentanyl, clonidine, and dexmedetomidine) during the intra- and postoperative periods⁽²⁰⁾. In our study, no statistically significant difference was observed in the inci-

dence of unfavorable possible complications and side effects between the 2 groups. Generally, the two most common side effects of dexmedetomidine are bradycardia and hypotension. In the present study, it was noted that dexmedetomidine was linked to intraoperative minor complications more than in the control group, although statistically insignificant, and was easily treated. The positive safety profile of neonatal SA is well-documented in infants and children. Complication rates are low, oxygen desaturation, and bradycardia occurring at rates of <1%, and <2%, respectively⁽²¹⁾. In Yang et al desaturation, hypotension, and bradycardia were reported, but with much lower percentages. This is attributed to the relatively larger sample size⁽²²⁾. It was observed that using dexmedetomidine was associated with bradycardia, furthermore, the higher the dose the higher the risk for experiencing bradycardia. However, Su et al reported bradycardia in 4.3% of neonates after open heart surgery where continuous infusion of dexmedetomidine was administered⁽²³⁾. Bradycardia was also reported to be 18% among infants who underwent cardiac surgeries and received 0.5 µg/kg/min of dexmedetomidine via continuous infusion⁽²⁴⁾. This was also supported by Shaikh and Dattatri 2014 as they found the incidence of bradycardia when 10 µg of dexmedetomidine was 1.33%. Hypotension in our study occurred in 4.3% of patients. This is similar to findings from Shaikh and Dattatri, where hypotension occurred in 3.3% of patients who received 5 and 10 µg of dexmedetomidine⁽²⁵⁾. This happens because low doses of dexmedetomidine in children lead to central sympatholytic, and subsequent systemic hypotension⁽²⁶⁾. In our study, desaturation was

reported in 8.7% of patients. Previous studies admitted the effect of dexmedetomidine but with varying degrees. For instance, Sulston et al reported that a much lower incidence rate of desaturation while using dexmedetomidine is 0.44%. Contradictory results from Hoorn et al revealed an incidence of 10% for desaturation (27, 28). Scientists believe that dexmedetomidine has an advantage over other sedative drugs in minimizing episodes of desaturation in children with obstructive sleep apnea. It is believed that dexmedetomidine is one of the least sedatives that can cause respiratory depression⁽²⁹⁾. In our study, apnea was presented in only 4.3% of patients who received dexmedetomidine. A lower incidence 1.6% was noticed among patients from Hoorn et al study. That is why they are usually given to patients with obstructive sleeping apnea during different procedures such as MRI^(28,29). However, there were no cases experienced high spinal block, nausea, vomiting, or delay in breast feeding in our study. In a systemic review and meta-analysis, Shen et al reported that the use of intrathecal dexmedetomidine during cesarean section enhanced the effect of local anesthetic without increasing the drug-related side effects. Also, Koch et al claimed that serious complications such as high spinal block, hematoma, infection, and neurologic deficits are extremely rare with dexmedetomidine^(14,30).

Conclusion

The addition of 0.3µg/kg dexmedetomidine to intrathecal hyperbaric bupivacaine was safe and efficient in infants undergoing infra-umbilical surgeries. The study presents optimistic results regarding the introduce

tion of dexmedetomidine as an adjuvant to intrathecal hyperbaric bupivacaine to achieve better, safer, and more efficient anesthesia during minor surgeries in infants. However, further studies on a larger scale of infants would be preferable, in addition to the inclusion of infants undergoing major surgeries as well.

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