Efficacy of intravenous sedation by Dexmedetomidine versus Propofol for caudal anesthesia in children undergoing lower abdominal surgery

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Abstract: Background: Caudal anesthesia is an important pediatric regional anesthetic technique, which can be used for many operative procedures; it is remarkably safe and relatively easy to learn. Mostly all caudal blocks are performed combined with general anesthesia, caudal block in sedated; spontaneously breathing infants and children is considered a safe alternative to general anesthesia alone. **Methods:** A total of 66 children of both sex aged 2-6 years of American Society of Anesthesiologists grade (ASA) I and II, posted for elective lower abdominal surgery were randomly divided in to two groups *(n* = 33 each) to receive either dexmedetomidine (IV) infusion (loading 1 µg/kg over 10 min followed by 0.2–0.6 µg/ kg/h) or Propofol (IV) infusion (loading dose 750 µg/kg followed by 12.5–75 µg/kg/min). All patients in both groups were received premedication atropine IV (0.01-0.02 mg/kg) and fentanyl IV (1 µ/kg). Inadequate sedation was defined as difficulty in completing the caudal block procedure because of movement of the child. The children who were inadequately sedated were given a single dose of midazolam 0.1 mg/kg in both groups intravenously (IV) as rescue doses. Baseline vital parameters: heart rate (HR), mean blood pressure (MBP), oxygen saturation (SPO_2) and respiratory rate (RR) were recorded during the study. Nasal mask was applied, and supplemental oxygen was administrated at 4L/min throughout the procedure. The rate of infusion titrated to maintain a sedation score of 3 on University of Michigan Sedation Scale (UMSS) throughout the surgery. Patient data, ASA class, surgical procedure, and baseline cardio-respiratory variables were similar between groups. **Results:** Six patients were excluded from the study due to inadequate caudal block. General anesthesia had been administered in these six patients. The onset and recovery from sedation were significantly earlier with propofol in compare with dexmedetomidine, the requirement for rescue drug (midazolam) was higher in Propofol group. Heart rate decreased significantly in Group I (dexmedetomidine) while mean arterial pressure decreased significantly in Group II (propofol)**. Conclusions:** Dexmedetomidine provided adequate sedation in most of the children aged 2– 6 years without hemodynamic or respiratory effects during caudal anesthesia in children undergoing lower abdominal surgery.

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1. Introduction

Caudal anesthesia is an important pediatric regional anesthetic technique, which can be used for many operative procedures; it is remarkably safe and relatively easy to learn. It is the most commonly performed regional anesthetic procedure in infants and children undergoing inguinal, anorectal, lower abdominal and lower extremity surgery procedures [1,2].

Mostly all caudal blocks are performed combined with general anesthesia, caudal block in sedated, spontaneously breathing infants and children is considered a safe alternative to general anesthesia alone. Only few studies have been published on caudal anesthesia as a sole anesthetic technique [3].

The ideal pediatric sedative drug should maintain a patient's ventilation, provide hemodynamic stability, patient immobility, and allow easy drug titration. It should also ensure rapid anesthetic induction and recovery while producing minimal side effects such as nausea, vomiting, dysphoria, [4].

Dexmedetomidine has a mechanism of action distinctively different from other anesthetics and sedatives. It is a highly selective α2-agonist, which acts on α2-adrenergic receptors in the locus coeruleus, providing relatively fast onset of sedation resembling natural sleep, with minimal respiratory depression. Dexmedetomidine has no known active or toxic metabolites and has been used safely in children and also in preterm neonates, even at very high doses [5].

On the other hand, Propofol (2,6-disopropylphenol) is a short acting, intravenous (IV) administered hypnotic agent. Bolus Propofol is used for short procedural sedation, whereas a continuous infusion may be employed for prolonged, motionless sedation. It should be used in adjunct with other

medications such as fentanyl or ketamine for painful procedures because Propofol has no analgesic effect. Propofol is a global central nervous system depressant. It potentiates GABA receptor activity, inhibits NMDA receptors, and modulates calcium influx through slow calcium ion channels [6].

Propofol has been the gold standard of intraoperative sedation due to its rapid onset and offset of action and easy titration when it used as continous infusion, but its major disadvantage is the depressant action on the patient's hemodynamics and respiration [7].

The aim of this study is to compare between the efficacy of dexmedetomidine and Propofol as a sedative agent before caudal anesthesia in children undergoing lower abdominal surgery.

2. Patients and Methods

After institutional review board (IRB) approval and written patients parents' consent, 66 pediatric patients with age range between 2- 6 years of both sexes with Physical status of ASA I or II undergoing elective lower abdominal surgery not exceeding more than 2 hours and scheduled to receive caudal block under sedation. The study was done in Zagazig University Hospitals between October 2017 to March 2018. Patients with known history of allergy to study drugs, difficult airway, BMI <5% or >95% of ideal body weight, infection or spinal abnormality, bleeding diatheses or cardiorespiratory diseases were excluded.

Patients were divided randomly using computer generated randomization table into two groups each of 33 patients according to the drug given for sedation. For all children, topical anesthesia with 2.5% lidocaine and prilocaine 2.5% (EMLA cream) was obtained in the sacral region and non-dominant hand 1 hr pre-operative. Venous access was secured on the non-dominant hand of every patient using 22 G cannula. All patients received Ringer's lactate at an infusion rate of 10 ml/ kg/h. All patients received atropine IV (0.01-0.02 mg/kg) and fentanyl IV (1 microgram/kg). A solution of dexmedetomidine (Precedex, Abbott laboratories, Lake Forest, IL60045, USA), was prepared as follows: 1 ml (100 µ) was added to 49 ml of normal saline to reach a concentration of 2 µ/ml. Another solution of Propofol 50 ml 1% was loaded undiluted in a 50 ml syringe. Dexmedetomidine group **(**Group I) received dexmedetomidine IV infusion (loading dose 1 µg/kg over 10 min followed by 0.2–0.6 µg/ kg/h). Propofol group (Group II), children received Propofol IV infusion (loading dose 750 µg/kg followed by 12.5–75 µg/kg/min). For all patients, nasal mask of O_2 100% was applied, and supplemental oxygen was administrated at 4L/min throughout the procedure. University of Michigan Sedation Scale (UMSS) table 1 was used to assist the level of sedation in both groups [8].

Table (1) University of Michigan Sedation Scale (UMSS)

Score	Characteristics
0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

The rate of infusion of either dexmedetomidine or propofol infusions was titrated to maintain a sedation score of 3 according to University of Michigan Sedation Scale (UMSS). Patient was considered to be ready for caudal block when the level of sedation reached score 3 on (UMSS). In case of inadequate sedation (UMSS score <3), IV midazolam 0.1 mg/kg was administered slowly to induce adequate sedation to complete the procedure and doses was recorded**.** In case of movement of patient during the operation, additive dose of midazolam administered (IV) and doses were recorded**.**

Caudal block: when the targeted level of sedation was reached, the patient was placed in the lateral position with both hips flexed, and the sacral hiatus was palpated. After sterile skin preparation, a short 22 gauge cannula was advanced at a 45° angle cephalad until a pop was felt as the needle pierces the sacrococcygeal ligament. The angle of the cannula was then flattened, the stylet was withdrawn and the cannula was advanced into the caudal space. Gentle aspiration was done to exclude blood or CSF. Local anesthetic using bupivacaine 0.25% 1 ml/kg was injected slowly, then the area of injection was covered. The patient was turned supine immediately after caudal block. The Successful neural blockade was assessed 10-15 min after caudal injection of local anesthetic and the block assumed successful when

some degree of motor paralysis in the legs was detectable and no reaction to skin prick in the relevant dermatomes occurred. In case of failed block, general anesthesia with endotracheal intubation was planned, and patients were excluded from the study.

Baseline data regarding mean arterial blood pressure (MAP), heart rate (HR), oxygen saturation (SPO_2), and respiratory rate (RR) were recorded and monitored continuously every 10 min interval starting just before the beginning of sedation process (by giving either dexmedetomidine or Propofol in group I or group II respectively) till the end of the surgery. Any adverse effect such as hypotension, bradycardia, nausea, and vomiting was also noted.

At the end of the surgery, dexmedetomidine or propofol was discontinued. The onset of sedation time was defined as the period of time between the beginning of study drug infusion and reaching reach score 3 on (UMSS). Recovery time was the time between discontinuation of drug infusion and reaching score 0 on (UMSS). Side effects (e.g., nausea, vomiting, respiratory depression) occurring during and/or after sedation were recorded.

3. Statistical analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. To compare means, independent sample t test was used when appropriate. Nonparametric test (Mann Whitney) was used to compare means when data was not normally distributed and to compare medians in categorical data. The level statistical significance was set at 5% (P<0.05).

4. Results

Patient data and type of operation in the current study showed that there were statistically non-significant differences between both study groups regarding age, weight a, sex and type of operation as shown in table (2). Six patients (3 cases from each group). were excluded from the study due to inadequate caudal block. General anesthesia had been administered in these six patients.

In adequate sedation

Inadequate sedation was observed in all children in Propofol group (n=30) and supplementary bolus dose of midazolam (0.1mg/kg) was needed to prevent movement of patients during caudal block procedure. In contrast, the dexmedetomidine group there was no need for any supplementary doses of midazolam. During intraoperative procedure no patient showed movement in both groups and there were no need for supplementary doses of midazolam.

Propofol group (group II) showed more rapid onset of sedation (highly significant) as compared to dexmedetomidine group (group I). Duration of infusion of both drugs during operation was comparable in both groups with no significant differences. Regarding the duration of recovery, Propofol group (groupII) showed shorter duration (highly significant) as compared to dexmedetomidine group (group I) as shown in table (3).

Table (2) Patient data of studied cases:

Patient characteristic, Procedure	**Group (I)** ***(n=30)***	**Group (II)** ***(n=30)***	**Significant**
Age (y) mean±SD	4.09±1.33	3.92±1.38	**NS**
Weight (Kg) mean±SD	16.42±2.41	16.15±2.56	**NS**
Sex (male to female)	20 /10	25/5	**NS**
Type of operation:			
-Inguinal hernia	25	19	**NS**
- Hypospadias	2	5	
-Orchidopexy	3	6	

Data are expressed as mean±SD. Group I (=dexmedetomidine group).
Group II (=propofol group), *n=number of cases* P >0.05= significant and N/S=non-significant.

Table (3) operative data of studied cases

	Group (I)	Group (II)	P value
Onset of sedation: mean±SD	15.06±1.9	10.0±1	<0.001
Duration of study drug infusion (min): mean±SD	39.0±7.97	40.17±11.9	**NS**
Duration of operation: mean±SD	20.77±8.09	25.1±11.89	**NS**
Duration of recovery: mean±SD	40.0±3.65	21.24±3	<0.001

Data are expressed as mean± SD.
P > 0.05 is significant. NS= non-significant.

There were statistically significant differences between both groups regarding mean blood pressure. Propofol group (group II) showed statically lower MAP compared to dexmedetomidine group (group I) at the following times of surgeries (after 30,40,50,60 and 70 min from the time of beginning of sedation as shown in figure (1).

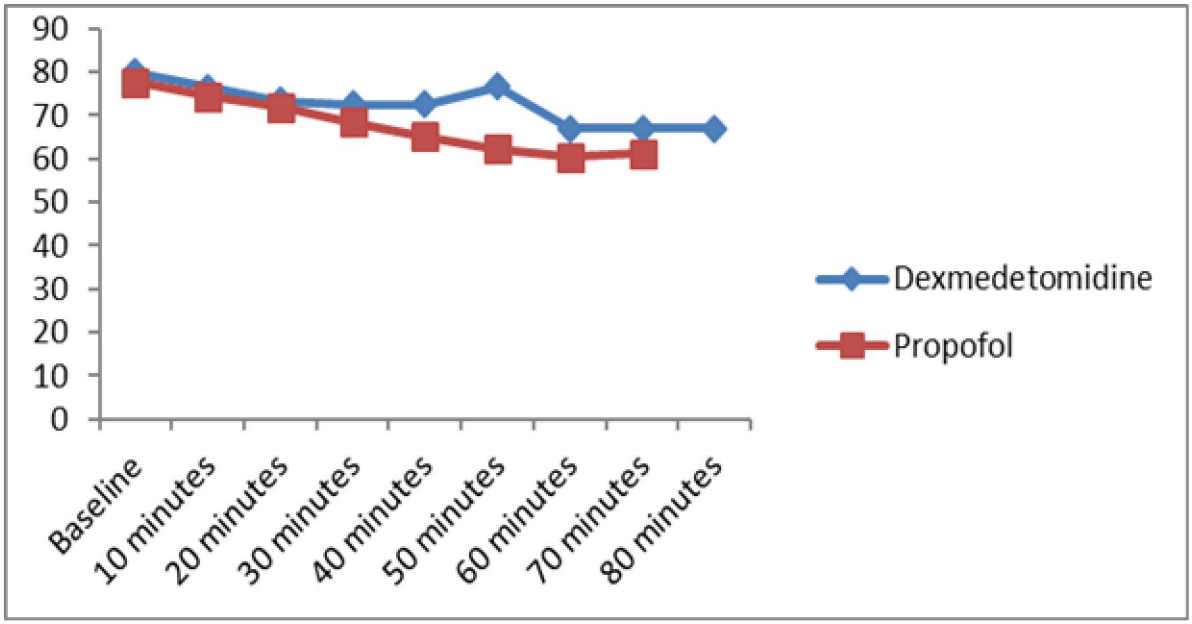

Figure (1) line gram showing change in mean blood pressure in study groups

There were statistically significant differences between both groups regarding mean heart rate (HR). Dexmedetomidine group (group I) showed statically lower (HR) compared to Propofol group (group II) at the following times of surgeries (after 10,20,30, 40 and 50 min from the time of beginning of sedation as shown in figure (2).

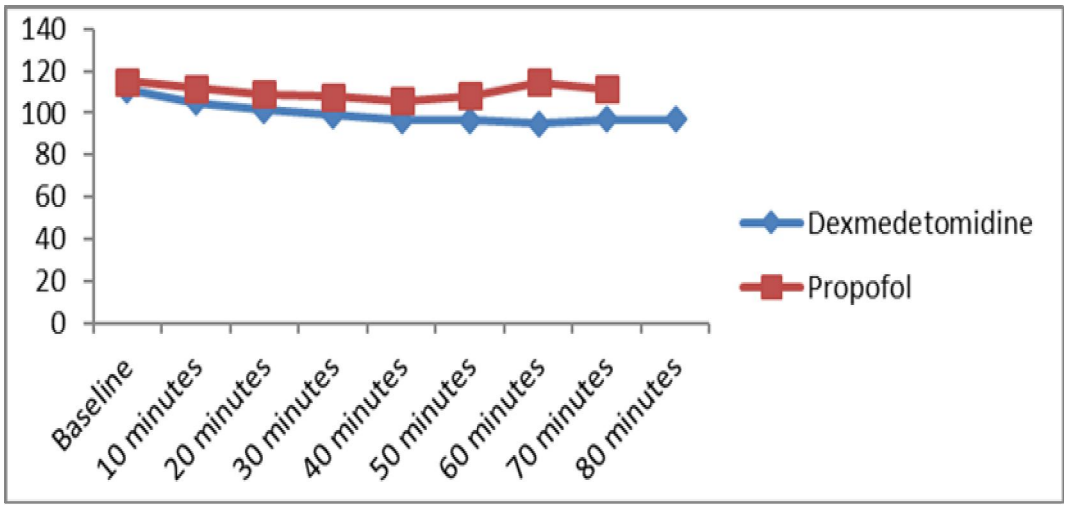

Figure (2) line graph showing change in Pulse in study groups

In spite of the significant differences between the two groups regarding MAP and HR during the different times of the study, none of these changes required medical resuscitation (the decrease in MAP and HR < 20% of basal level in both groups). Thereby, theses changes in MAP and HR in both groups were not considered as complication.

There were statistically non-significant differences between both groups regarding respiratory rate (RR) and Peripheral oxygen saturation (Spo_2) from the time of beginning of sedation as shown in figure (3).

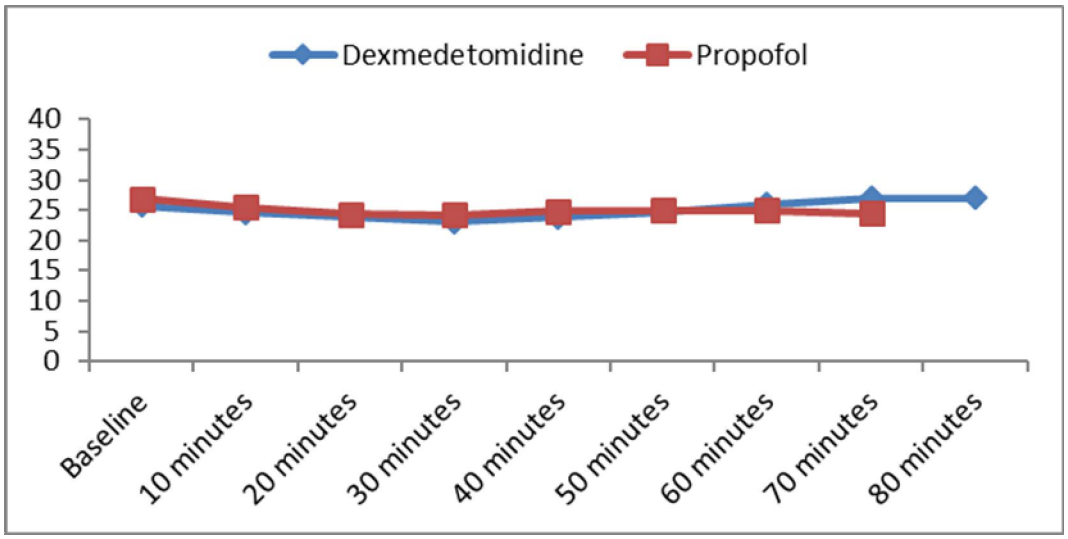

Figure (3) line graph showing change in respiratory rate in study groups

4. Discussion

The aim of the present study was to compare the efficacy of intravenous sedation by Dexmedetomidine versus propofol for caudal anesthesia in children undergoing lower abdominal surgery. The results obtained in the current study showed that.

These dose of dexmedetomidine (1µg/ kg as loading followed by 0.2– 0.6 µg/ kg/ h as maintenance) was enough to sedate child. That doses used in the current study are similar to doses used in Previous studies Hall et al. [9] and Tobias et al. [10] and had provided effective sedation.

Regarding propofol doses as (750 µg /kg as loading followed by 12.5–75 µg/kg/min as maintenance). patients in the current study did not reach the targeted level of sedation (score of 3 UMMS) at time of induction of sedation and all the patients in Propofol group (group II) need

supplementary bolus doses of midazolam (0.1mg/kg) to reach the targeted level of sedation.

Regard of time of onset of sedation in Propofol group which was around 10 min in this study results, this results was similar with study results by Khurana et al. [11].

Hasan et al. [12] study results showed the propofol's onset was shorter than the current study results.

Regard of Propofol time of recovery Bloomfield et al. [13] showed similar results to the current study.

Also in this current study results correlate with Hasan et al. [12] that showed recovery time of Propofol around 20 min, when Propofol used for Deep sedation for children undergoing ambulatory magnetic resonance imaging of the brain.

Arian et al. [14] reported onset sedation induction around 25 min and a recovery time around 34 min with dexmedetomidine. In the current study, the onset were around 15 min and the recovery time was around 40 min. this might be attributed to the difference in age groups as Arian studied adult while the current study was applied on children. Moreover, patients in the current study were given fentanyl (1μ/kg) as premedication.

Koroglu et al. [15] showed that recovery time from dexmedetomidine around 19 min in children undergoing magnetic resonance imaging examination, which made that results not in correlate to this current study results.

Dexmedetomidine is known to decrease sympathetic outflow and circulating catecholamine levels and would therefore be expected to cause decreases of MAP. In this current study, there was decrease in mean arterial pressure (MAP) but less than that in propofol group (group II)

Ebert et al. [16] found that intravenous boluses of dexmedetomidine show decreases in BP after small boluses (0.25–1 μg/kg). Also Talke et al. [17] found that Perioperative use of α_2 agonists is associated with hypotension, that results correlate current study results.

Previous study by Kumar et al. [18] showed that the MAP in Dexmedetomidine Group remained somewhat constant till the end of surgery during Sedation in Brachial Plexus Block, the Kumar study results were not correlate in this current study results which showed decrease in MAP during the procedure.

It has been reported that Patients who were administered Propofol experienced a decrease in MAP. The fall in MAP could be due to the powerful inhibitory effect on the sympathetic outflow Propofol has Shah et al. [19], These results was similar to current study. In Propofol group, infusion cause more decrease in MAP in compare with Dexmedetomidine group.

Arain et al. [14] also reported that MAP was significantly reduced when propofol used during the intraoperative period and the reduction was significantly less in patients receiving dexmedetomidine.

In contrary to this current study, the results of Usher et al. [20] Cardiovascular stability was demonstrated by no change in systolic blood pressure when Propofol used as total intravenous anesthesia for MRI in children.

Heart rate (HR) was significantly lower of baseline in Group I (dexmedetomidine) 13% when compared to Group II (propofol) 6% at 40 minutes. This might be due to the sympatholytic and vagal mimetic effect of dexmedetomidine. The results are similar to the studies done by Mahmoud et al. and *Mason* et al. [21, 22].

Also this current study results agreement with De Jonge et al. [23], which study the Participation of Cardiac Presynaptic ~2-Adrenoceptors in the bradycardiac effects of Clonidine and Analogues.

As regard changes in heart rate (HR) during sedation in propofol group, in this current study propofol group (II) showed decrease in heart rate (HR), but less than which occurred in dexmedetomidine group (I).

The results of this study also in correlation with Khurana et al. [11] who found propofol group showed more decrease in heart rate in compare with in midazolam group during sedation in regional anesthesia.

Regarding respiratory rate (RR) changes in this current study, there was clinically insignificant changes occurred in RR with dexmedetomidine.

The unique feature of dexmedetomidine is deep sedation without respiratory compromise. Satisfactory results have been found when dexmedetomidine has been used for sedation during regional and local anesthesia in the studies by Mason et al. and Manne et al. [24,25], the results in the current study were consistent with these studies.

Also Some authors have reported that dexmedetomidine did not affect RR, Spo2, and ETco2 Hall et al., Al-Mustafa et al. and Venn et al. [9,26,27].

Few reports describe the incidents of respiratory depression during infusions of propofol for sedation Lee et al. [28] However, In the present study, there were clinically insignificant decrease in RR during propofol infusion.

Also the current study results had similar results by Ebert et al. and Venn et al. [16,27] which found no significant differences in respiratory rate with intravenous administration of dexmedetomidine.

Regard changes in peripheral SpO_2 levels, there was no difference in peripheral SpO_2 levels in both the

groups in the intraoperative period. The $SpaO_2$ values in all the patients in both the groups were above 95%.

In this current study, there were no significant side effects after dexmedetomidine and hemodynamic changes were generally mild and self-limited. Also, there were No side effects such as nausea, vomiting, or dysphoria were observed in either group during or after sedation.

Conclusion

In conclusion, Propofol had more rapid onset and recovery of sedation, as compared to Dexmedetomidine group, also the dose in Propofol group need supplementary bolus dose of midazolam to reach the target level of sedation; however, no need for midazolam in Dexmedetomidine group. So in spite of delay onset and offset of Dexmedetomidine, it may offer more favorable conditions as a sole than propofol during sedation for caudal block in children undergoing lower abdominal surgery.

References

1. Schuepfer, Guido, Christoph Konrad, Joachim Schmeck, Gert Poortmans, Bruno Staffelbach, et al. "Generating a learning curve for pediatric caudal epidural blocks: an empirical evaluation of technical skills in novice and experienced anesthetists." *Regional anesthesia and pain medicine* 25, no. 4 (2000): 385-388.
2. Sanders, J C. "Paediatric regional anaesthesia, a survey of practice in the United Kingdom." *British journal of anaesthesia*89, no. 5 (2002): 707-710.
3. Brenner, L, S C Kettner, P Marhofer, D Latzke, H Willschke, et al. "Caudal anaesthesia under sedation: a prospective analysis of 512 infants and children." *British journal of anaesthesia* 104, no. 6 (2010): 751-755.
4. Frankville, David D, Robert M Spear, and John B Dyck. "The dose of propofol required to prevent children from moving during magnetic resonance imaging." *Anesthesiology* 79, no. 5 (1993): 953-958.
5. Bong, Choon L, Angela SH Yeo, Teddy Fabila, and Josephine SK Tan. "A pilot study of dexmedetomidine sedation and caudal anesthesia for inguinal hernia repair in infants." *Pediatric Anesthesia* 26, no. 6 (2016): 621-627.
6. Srinivasan, Mythili, and Douglas W Carlson. "Procedural sedation by pediatric hospitalists: analysis of the nature and incidence of complications during ketamine and nitrous oxide sedation." *Hospital Pediatrics* 3, no. 4 (2013): 342-347.
7. Ghali, Ashraf, Abdul Kader Mahfouz, Tapio Ihanamäki, and Ashraf M. El Btarny. "Dexmedetomidine versus propofol for sedation in patients undergoing vitreoretinal surgery under sub-Tenon's anesthesia." *Saudi journal of anaesthesia* 5, no. 1 (2011): 36.
8. Malviya, S, T Voepel-Lewis, A R Tait, S Merkel, K Tremper, and N Naughton. "Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS)." *British journal of anaesthesia* 88, no. 2 (2002): 241-245.
9. Hall, Judith E, Toni D Uhrich, Jill A Barney, Shahbaz R Arain, and Thomas J Ebert. "Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions." *Anesthesia & Analgesia* 90, no. 3 (2000): 699-705.
10. Tobias, Joseph D, and John W Berkenbosch. "Initial experience with dexmedetomidine in paediatric ‐ aged patients." *Pediatric Anesthesia* 12, no. 2 (2002): 171-175.
11. Khurana, Priyanka, Ankit Agarwal, R K Verma, and P K. Gupta "Comparison of midazolam and propofol for BIS-guided sedation during regional anaesthesia." *Indian journal of anaesthesia* 53, no. 6 (2009): 662.
12. Hasan, Rashed A, Jay R Shayevitz, and Vipul Patel. "Deep sedation with propofol for children undergoing ambulatory magnetic resonance imaging of the brain: experience from a pediatric intensive care unit." *Pediatric Critical Care Medicine*4, no. 4 (2003): 454-458.
13. Bloomfield, Eric L, Thomas J Masaryk, Audrey Caplin, Nancy A Obuchowski, Armin Schubert, John Hayden et al. "Intravenous sedation for MR imaging of the brain and spine in children: pentobarbital versus propofol." *Radiology*186, no. 1 (1993): 93-97.
14. Arain, Shahbaz R, and Thomas J Ebert. "The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation." *Anesthesia & Analgesia* 95, no. 2 (2002): 461-466.
15. Koroglu, A, S Demirbilek, H Teksan, O Sagır, A K But, and M O Ersoy. "Sedative, haemodynamic and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results." *British journal of anaesthesia* 94, no. 6 (2005): 821-824.
16. Ebert, Thomas J, Judith E Hall, Jill A Barney, Toni D Uhrich, and Maelynn D Colinco. "The effects of increasing plasma concentrations of dexmedetomidine in humans." *Anesthesiology: The Journal of the American Society of Anesthesiologists* 93, no. 2 (2000): 382-394.

17. Talke, Pekka, Richard Chen, Brian Thomas, Anil Aggarwall, Alexandru Gottlieb, et al. "The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery." *Anesthesia & Analgesia* 90, no. 4 (2000): 834-839.
18. Kumar, Amarjeet, Chandni Sinha, Ajeet Kumar, and Poonam Kumari. "The effect of intravenous dexmedetomidine compared to propofol on patients hemodynamics as a sedative in brachial plexus block: A comparative study." *Anesthesia, essays and researches* 11, no. 1 (2017): 201.
19. Shah, Pratibha Jain, Kamta Prasad Dubey, Kamal Kishore Sahare, and Amit Agrawal. "Intravenous dexmedetomidine versus propofol for intraoperative moderate sedation during spinal anesthesia: a comparative study." *Journal of anaesthesiology, clinical pharmacology* 32, no. 2 (2016): 245.
20. Usher, Andrew G, Ramona A Kearney, and Ban CH Tsui. "Propofol total intravenous anesthesia for MRI in children." *Pediatric Anesthesia* 15, no. 1 (2005): 23-28.
21. Mahmoud, Mohamed, Joel Gunter, Lane F Donnelly, Yu Wang, Todd G Nick, et al. "A comparison of dexmedetomidine with propofol for magnetic resonance imaging sleep studies in children." *Anesthesia & Analgesia* 109, no. 3 (2009): 745-753.
22. Mason, Keira P, David Zurakowski, Steven Zgleszewski, Randy Prescilla, Paulette J Fontaine, et al. "Incidence and predictors of hypertension during high‐dose dexmedetomidine sedation for pediatric mri." *Pediatric Anesthesia* 20, no. 6 (2010): 516-523.
23. De Jonge, A, P B M W M Timmermans, and P A Van Zwieten. "Participation of cardiac presynaptic α 1-Adrenoceptors in the bradycardiac effects of clonidine and analogues." *Naunyn-Schmiedeberg's archives of pharmacology* 317, no. 1 (1981): 8-12.
24. Mason, Keira P, Steven E Zgleszewski, Randy Prescilla, Paulette J Fontaine, and David Zurakowski. "Hemodynamic effects of dexmedetomidine sedation for CT imaging studies." *Pediatric Anesthesia* 18, no. 5 (2008): 393-402.
25. Manne, Gourishankar Reddy, Mahendra R Upadhyay, and V N Swadia. "Effects of low dose dexmedetomidine infusion on haemodynamic stress response, sedation and post-operative analgesia requirement in patients undergoing laparoscopic cholecystectomy." *Indian journal of anaesthesia* 58, no. 6 (2014): 726.
26. Al-Mustafa, Mahmoud M, Izdiad Z Badran, Hamdi M Abu-alI, Bassam A Al-Barazangi, Islam M Massad, and SUBHI M. Al-Ghanem. "Intravenous dexmedetomidine prolongs bupivacaine spinal analgesia." *Middle East J Anesthesiol* 20, no. 2 (2009): 225-231.
27. Venn, Richard M, John Hell, and R Michael Grounds. "Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care." *Critical Care* 4, no. 5 (2000): 302.
28. Lee, Mi Hyeon, Ki-Hwan Yang, Choon Soo Lee, Hong Sik Lee, Sin Yeong Moon, et al. "The effect-site concentration of propofol producing respiratory depression during spinal anesthesia." *Korean journal of anesthesiology* 61, no. 2 (2011): 122-126.

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