Research Article

Effect of Nebulized dexmedetomidine on pediatric hepatic patients undergoing upper endoscopy; a randomized controlled trial

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ABSTRACT:

Background: Chronic hepatic patients are especial category causing distress to nursing for cannulation and preparation before follow up procedures as they have fragile veins or fibrosed in addition to difficult cannulation ,the bad clinical condition for day case procedures and the psychic trauma they had. Aim In this study we aim to assess the effect of nebulized Dexmedetomidine on sedation, face mask acceptance, emotional separation scores before upper endoscopy.

Methods: sixty eight children aged 4-16 years were randomly allocated into two equal groups to be premedicated with either nebulized dexmedetomidine (Group D) 2µg /kg-, or saline 0.9 same volume (Group S). The primary outcome was a five-point sedation score; parental separation anxiety scale; and mask acceptance scales on arrival in the endoscopy room 30 min after end of study drug administration. Secondary outcomes included: Emotional separation anxiety scale; and mask acceptance scales, secondary outcomes includes heart rate; time to discharge ;and Propofol dose.

conclusion there were significant difference regarding sedation, face mask acceptance emotional separation scores in favors of nebulized group with dexmedetomidine and also there were significant decrease in Propofol in dexmedetomidine group as well as heart rate .

Key words: perioperative anesthesic sedation- chronic hepatic pediatric patients –upper endoscopy.

Writing draft and idea,;Dr Nahla gaballa.

Endoscopist and collection of demographic data Dr.Tahany Abd Elhamid -Scientific revision; nahla gaballa.

INTRODUCTION

PATIENTS AND METHOD:

SAfter approval and informed consent from the local committee of anesthesia, I.C.U and pain management department and pediatric department at national liver institute, IRB 00194/2020 we studied sedation in (68) patients ASA II and cirrhotic pediatric patients undergoing upper gastrointestinal (GIT) endoscopy enrolled in this prospective ,randomized study .

Sample size estimation

Based on review of past literature (Hazem et al.,2020) who found that 20% of patients in group nebulized dexmedetomidine had excellent score of parental separation and face mask acceptance and no one in group nebulized ketamine had excellent score .Sample was calculated at power 80% to detect and confidence interval 95% .the calculated sample was 68 participants

Patients were classified in to two groups(all are fasting):

Group (D) with Dexmedetomidine nebulization.

Group (C) control cases with saline nebulization.

Patients included in the study:-

- patients ASA II and III .[1]
- Aged 4 years-16 year.

Exclusion criteria

- Neurologically and mentally affected children.
- Unwilling to participate.
- Hemodynamic instability.

As a premedication drugs will be prepared in 3 mL of saline 0.9% before administration by a standard hospital jet nebulizer via a mouthpiece, with a continuous flow of 100% oxygen at 6 L/min for 10 to 15 minutes (30 minutes before procedure). Treatment will be stopped when the nebulizer began to sputter. (There will be a surgical mask on the mask of nebulizer of the child for suspecting asymptomatic carriers of COVID -19 and the relative too)

Dose of Nebulized Dexmedetomine will be (2 µg/kg)

Data collected include age, sex, procedure performed, parental separation emotional score, hemodynamics,(heart rate ,oxygen saturation) just before procedure, recovery time.

Emotional state score[2]

1 Calm

2 Apprehensive, not smiling, tentative behaviour, withdrawn

3 Crying

4 Thrashing, crying with movement of arms and legs, resisting

Time needed for eligibility to discharge.

Sedation by Ramsay Sedation Scale which is a test of arousability. The RSS scores sedation at six different levels, according to how rousable the patient.

Ramsay Sedation Scale[3]

1.Patient is anxious and agitated or restless, or both.

2.Patient is co-operative, oriented, and tranquil.

3.Patient responds to commands only.

4.Patient exhibits brisk response to light glabellar tap or loud auditory stimulus.

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5.Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.

6.Patient exhibits no response.

The primary outcome is to compare, sedation before procedure, face mask acceptance and emotional separation score with dexmedetomidine on hepatic pediatric children undergoing upper endoscopy. Secondary out was the discharge time ,heart rate after nebulization ,Propofol dose.

Statistical analysis

Data were collected, tabulated, statistically analyzed using an IBM personal computer with Statistical Package of Social Science (SPSS) version 19 (SPSS, Inc, Chicago, Illinois, USA).where the following statistics were applied:

- Descriptive statistics: in which quantitative data were presented in the form of mean ( ), standard deviation (SD), range, and quality ative data were presented in the form numbers and percentages.

Analytical statistics: used to find out the possible association between studied factors and the targeted disease. The used tests of significance included:

*Chi-square test ($\chi 2$): was used to study association between two qualitative variables.

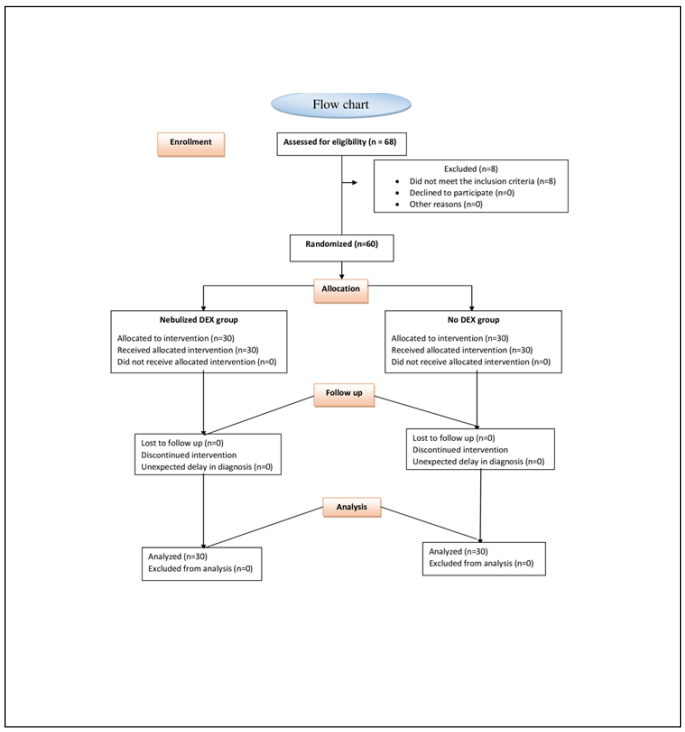
*Fischer exact test for 2 x 2 tables when expected cell count of more than 25% of cases was less than 5.

*Mann-Whitney test (nonparametric test): is a test of significance used for comparison between two groups not normally distributed having quantitative variables.

P value of >0.05 was considered statistically non -significant.

P value of <0.05 was considered statistically significant.

P value of <0.001 was considered statistically highly significant.



Results

60 patients out of 68 were enrolled in the study while 8 patients were excluded because of (refusal /on inotropic support/Down cases).

From table (1) there were no significant differences regarding demographic data of patients. No difference at all regarding saturation which was 100%.

When comparing sedation between dexmedetomidine group (1), with non dexmedetomidine group (2) 30 min after nebulization and before endoscopy 60% of non dexmedetomidine group were oriented and co-operative and the rest 40% were anxious, while in the dexmedetomidine group 90% of cases significantly responded to command and only 10% co-operative and oriented ,the nebulized group showed no anxious patients figure (1).

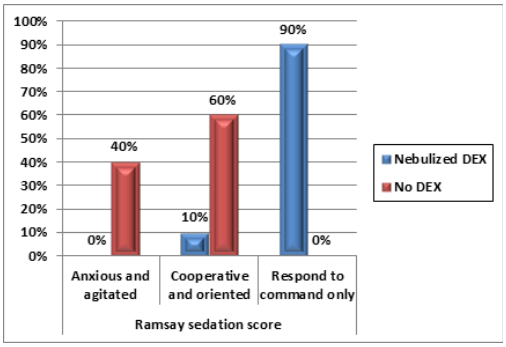


Figure 1) *Percentage distribution of sedation score among the studied groups.*

Regarding the easiness of child separation from the parents the nebulized group showed 30% in the fair score ,36.7 %in the good score and 33.3% in the excellent score while non -nebulized group showed 50% in the fair score,46.7% in the good score and 3% in the excellent score; figure (2).

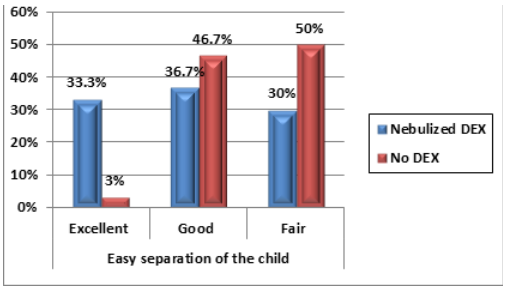


Figure 2) *Percentage distribution of easy separation of the child among the studied groups.*

With face mask acceptance the nebulized group showed 40% excellent score, 46.7% good score, and 13.3% in the fair score while in the non-nebulized group 46.7% in the good score as the other group, 30% in the fair score and 23.3% for poor score.

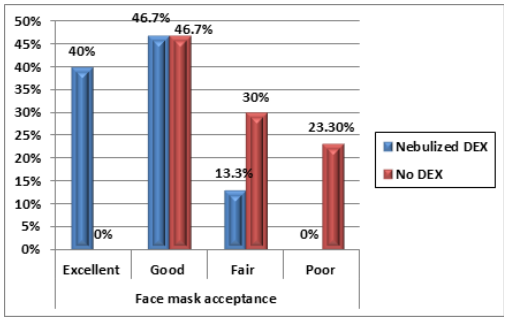


Figure 3) *Percentage distribution of face mask acceptance among the studied groups*

When comparing the nebulized group with the non –group, there was significant decrease in heart rate in the nebulized one ,significant decrease in Propofol consumption in nebulized group ,and no statistical significance between both groups regarding time to discharge ,table (2).

Table 2.Comparison between studied groups regarding heart rate and dose of profodol and recovery time

Data are presented as mean (SD) – median **High significant p value is Mann Whitney test

Discussion

Being a child with a chronic disease means frequent visits to the hospital with frequent laboratory tests withdrawal. Cannulation and upper endoscopy are daily procedures with increasing difficulty in pediatric / critically ill /hepatic patients because of this repeated cannulation, weak veins, varices and bleeding tendency, this category should have special care for managing psychic trauma and facilitating the process of endoscopy .Pre anesthetic medications are usually used to decrease the anesthetic dose, in this search we aim to decrease the added sufferings for chronic patients. Facing a child with fear, pain, anger with non-pharmacological method (distraction technique) in a trial to convince the child to co-operate seems to be impossible some times. Choosing sedation in a painless way is applicable especially if it can be applied in the presence of parents with unnoticed medical supervision. [4] In 1999, Dexmedetomidine has been registered in USA [5] as a selective and potent 2-adrenoceptor agonist that is used for its anxiolytic, sedative, and analgesic properties (Precedex®; Hospira, Lake Forrest, IL, USA). It acts on locus cerelus where the brain activity appears in electroencephalogram resembling natural sleep, so that Patients are sedated and at same time easily aroused. [6] In 2003 it was additionally approved by the US Food and Drug Administration and appeared useful in multiple off-label applications such as pediatric sedation, intranasal or buccal administration, and used as an adjuvant to local analgesia techniques. [7] [8]

Dexmedetomidine given intravenously is highly protein bound and metabolized in liver into an inactive form, and chronic hepatic patients had impaired liver function in the form of hypoalbuminemia, For Dexmedetomidine, prolonged [9] as well as shortened elimination half-lives have been reported for patients with hypoalbuminemia [10] . In the "well-stirred" liver model, a drug with a high extraction ratio, liver blood flow is the most important factor governing hepatic clearance . Changes in plasma protein levels are not supposed to increase drug clearance or minimally affect the clearance in general [11]. .The net result is that changes in Dexmedetomidine clearance result from the changes of cardiac output which affect liver blood flow.

When orally given its bioavailability is 16% , With extravascular administration, one can avoid the high peak plasma levels normally seen after IV administration and the extensive first pass metabolism with oral administration . We choose nebulization to provide rapid drug absorption through nasal, respiratory, and buccal mucosa, and allow bioavailability of 65% through nasal mucosa and 82% through buccal mucosa. [12] [13].

Effects of Dexmedetomidine besides sedation includes decreasing the stress response to intubation; and has been used as a sole anesthetic for infants requiring general anesthesia for direct laryngoscopy with preserving spontaneous ventilation and that was quiet adequate for stabilizing hemodynamic and respiratory profiles [14].

Regarding the spectrum of conditions that requires sedation and analgesia in pediatric population. Ineffective treatment of pain may result in physiological and behavioral responses that can adversely affect the developing nociceptive system[15] .To detect the anxiety of the child it is sometimes enough to observe their faces, heart rate, and of course behavior when white medical staff becomes nearer.

Oral pediatric sedation, intranasal or buccal administration was approved by FDA in 2003. Administration is widely accepted as efficacious, economic, and convenient among all routes of conscious sedation. Intranasal site is highly vascularized and very permeable for drug administration in order to ensure rapid absorption into systemic circulation. The administration of the drugs is well tolerated, effective, and fast acting. [16] .

The children in our study were having chronic liver disease, some have vascular decompensation, some complain of corrosive injury or gastropathy and bleeding. Because of their sufferings and recurrent need for follow up by endoscopy and post traumatic shock after separation from parents ,and as midazolam causes delayed recovery in hepatic patients ,we decided to try Dexmedetomidine versus saline to observe the pros and cons with it.

Practically intranasal and buccal routes are the most commonly used in pediatric sedation .In a study by Yao et al, intranasal administration of 1–4 μg/kg Dexmedetomidine in healthy children sedated them within 15-45 min and observed for 1-2 hours later , attenuating stress response of intubation and even reducing MAC of Sevoflurane[17]. In our study we choose the nebulized form for better tolerance, and easiness to provide with presence of parents and start assessment 30 min after nebulization just before procedure.

Regarding the choice of the technique McCormick et al. compared inhalation of nebulized midazolam versus intranasal midazolam administration. They concluded that nebulization is better tolerated [18].

Recently, Li et al [19] . compared 3 μg/kg intranasal Dexmedetomidine, administered by atomizer or drops in children less than 3 years of age. Both were equally effective. The only disadvantage for this drug was relatively slow onset of effect [20] When comparing IV 1 μg/kg Dexmedetomidine with intranasal 1 μg/kg dexmedetomidine, onset times were 15–20 and 30–45 min, respectively .

We found(excellent) sedation ,Emotional separation score and face mask acceptance scores in nebulized group ,while in saline group the three scores were (good)scores and it was statistically significant , the cause that most of non -nebulized group scores were not poor that most of the children were older enough to co-operate and accepted being chronic patients with frequent follow up visits. (Poor) scores and crying children were five years or less and newly discovered while same age with the nebulized drug showed better outcome. The actual difference was in the emotional score which states that with dexmedetomidine in all ages they were more comfortable and even smiling while on their way to endoscopy.

In healthy pediatrics Zanaty and Metainy compared inhaled nebulized dexmedetomidine (D) and ketamine (K), and a low dose combination (DK) in pediatric outpatient dental surgeries. The sedation level at 30 min was significantly greater in Group DK than in Group K or Group D with no difference between D and K groups. There were no significant differences between groups in the ease of parental separation, ease of venepuncture, or face mask acceptance. They concluded that a nebulized combination of low dose ketamine and dexmedetomidine produced more satisfactory sedation and provided a smoother induction of general anesthesia than nebulized ketamine or dexmedetomidine alone [2].the same with Preschool children premedicated with nebulized dexmedetomidine had more satisfactory sedation, shorter recovery time, and less postoperative agitation than those who received nebulized ketamine or midazolam [21].

In our study we did not find any significant difference in discharge time between both dexmedetomidine nebulized group and saline control, which may be explained by different length of the procedure and the need for intubation before endoscopy for safety issues in some cases with delayed recovery even in nebulized one.

One RCT by Gyanesh, P et al compared the effects of nebulized Dexmedetomidine versus nebulized ketamine and their combination on mask induction and satisfactory sedation in children undergoing dental surgeries. The results find that nebulized combination of low-dose ketamine and Dexmedetomidine has more satisfactory sedation and provide a smoother induction of general anesthesia, more rapid recovery than ketamine or Dexmedetomidine alone [2] .the same found by abdel-gaffar et al who compared nebulized dexmedetomidine, ketamine ,midazolam for bone marrow biopsy in preschool children [21].

As recovery depends on how much sedatives and anesthesia we were given even cases sedated by Dexmedetomidine had small Propfol dose for facilitating endoscopy , but in general recover time for patients ranged from 15-30 min , while time to discharge was affected by time of procedure , the need for further Propofol boluses, chest condition ,side effects like vomiting ,time needed to follow bleeding in children undergoing bandage .We need further research regarding using Dexmedetomidine alone for such category.

Regarding Propofol dose needed in our study ,it was significantly low in dexmedetomidine nebulized group , that was also the same finding by Jang et al. who observed the needed dose of Propofol for laryngeal mask insertion in a group premeditated with dexmedetomidine and saline control and Although heterogeneity in study populations, dosing regimens, and timing of drug administration ,a reduction in the Propofol requirement is found when co-administered[22].

One RCT addressed this subject in 115 elderly (aged >65 years) patients undergoing orthopedic surgery. They more frequently found a calm state at emergence in groups receiving dexmedetomidine compared with placebo, as an adjuvant to total IV or sevoflurane anesthesia [23]

How long does a child need to be observed in after short post-procedural sedation?

Dose ,route of administration,and patient metabolism determines the duration of action of sedative effects .whether hepatic or not the child should be back to how he was before sedation(speech, motor, cognitive).The TREKK guidelines published the following recommendation: "Monitor until the patient is able to perform their baseline (developmentally appropriate) activities ,they should be able to walk or tolerate oral fluids without emesis with their caregivers at home [24] .

Finally, uncertainty remains about the maturation of the hepatic clearance in neonates/children and therefore thoroughly validated age-based dosing regimens are lacking but till now we can proceed to use safely with expanded research.

Conclusion

The more the care you give to any patient before procedures (psychological preparation and sedation),the better the outcome and less consumption of drugs , we cannot stop progressive liver diseases from going on ,but we can delay complications by better care and less pain , our mission not to add years to life but to add life to years .

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