Prolongation of Caudal Analgesia in Pediatric Surgery: Comparison between Dexmedetomidine, Clonidine, Tramadol, and Fentanyl.

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ABSTRACT

BACKGROUND: This study was designed to investigate whether the addition of dexmedetomidine or clonidine or tramadol or fentanyl to bupivacaine for caudal blocks in children would prolong postoperative pain relief and reduce the need for additional analgesics thus allowing single shot caudal analgesia to be recommended for surgery lasting more than 90 min.

METHODS: 112 ASA I or II male and female children, aged 3–10yr, and their body weight between 10 –30kg, undergoing elective surgical procedures expected to last more than 90 min, and scheduled to receive general anesthesia combined with caudal extradural block were recruited. Anesthesia was induced with halothane and 60% nitrous oxide in oxygen and maintained with isoflurane (0.6 MAC corrected for age), using standard monitoring. Children were allocated randomly to one of five groups to receive a caudal injection: Group B received 1 ml/ kg of a mixture of equal parts of 0.25% bupivacaine, and 1% lidocaine; group D received the same mixture of local anesthetics plus dexmedetomidine 1.5µg/ kg; group C received the same mixture of local anesthetics plus clonidine 2µg/ kg; group T received the same mixture of local anesthetics plus tramadol 2mg/ kg; and group F received the same mixture of local anesthetics plus fentanyl 2µg/ kg. Postoperative monitoring of SpO2, hemodynamics, with assessment of analgesia, sedation, and development of any side effects until 6 h after caudal block

RESULTS: Duration of analgesia was significantly longer in the four groups who received additives compared with control group:(245 ± 10) min in group B, (347 ± 13) min in group D, (350 ± 10) min in group C, (280 ± 20) min in group T, and (275 ± 15) min in group F (P < 0.05). In groups D and C, the mean duration of analgesia was significantly longer than groups T and F (P < 0.05) , but no significant differences were observed between groups D and C. Hemodynamics and level of sedation were similar in the five groups. Postoperative vomiting and transient oxygen desaturation were observed only in children who received extradural fentanyl.

CONCLUSIONS: for caudal blockade, the addition of dexmedetomidine 1.5µg/ kg, or clonidine 2µg/kg, or tramadol 2mg/ kg, or fentanyl 2µg/ kg to 0.25% bupivacaine significantly prolongs the duration of analgesia and reduces the postoperative analgesic requirements with preserved hemodynamic stability and lack of sedation, thus allowing single shot caudal anesthesia to be recommended for surgery lasting 90–150 min. Dexmedetomidine and clonidine have an equipotent effect on the characteristics of the block , and they may be the drugs of choice to prolong duration of caudal anesthesia provided by a single injection in children.

Introduction:

Caudal analgesia is widely used in pediatric anesthesia practice for orthopaedic, lower abdominal, and genitourinary surgical procedures, with the advantages of ease of application, reducing the requirement of inhalational anesthetics, and providing effective postoperative analgesia. [1] These benefits are especially important in ambulatory and same-day surgery patients because it reduces analgesic requirements and facilitates early discharge.

Bupivacaine is the most commonly used local anesthetic in caudal anesthesia in paediatric practice, and it provides reliable, long-lasting anesthesia and analgesia when given via the caudal route. However, the mean duration of surgical analgesia provided by local anaesthetics is limited and thus single shot caudal anaesthesia is indicated only for surgery expected to last less than 90 min. [2]

In longer surgical procedures, insertion of an extradural catheter may be required to achieve sustained analgesia. However, placement of an extradural catheter is time-consuming and more expensive than single shot caudal block, and may be associated with various technical problems such as difficulty in insertion, vascular damage or leaks. [3]

To overcome these problems, various drugs have been added to local anaesthetic solutions to prolong the duration of caudal anaesthesia provided by a single injection.

The caudal administration of 0.02 mg/kg morphine in combination with 0.66 mL/kg bupivacaine 0.25%, seems to provide superior analgesia, and also prolongs caudal analgesia but carries with it the risk of respiratory depression. [4]

Also, ketamine1 mg/kg ; produces analgesia after epidural administration and improves the duration and quality of analgesia provided by bupivacaine in caudal blocks; however, because of possible neurotoxicity of preservatives added to commercially available morphine and ketamine preparations, the drugs are not recommended for epidural or spinal administration. [5]

Dexmedetomidine is a potent and highly selective α_2–adrenoreceptor agonist. It has an α_2/α_1 selectivity ratio which is eight times higher than that of clonidine. It has sedative-hypnotic, anxiolytic, and analgesic, anesthetic-reducing and sympatholytic effects. In contrast to other agents, the sedation and analgesia produced by dexmedetomidine are achieved without significant respiratory or haemodynamic compromise. [6] Analgesic properties were found when epidural or intrathecal dexmedetomidine was used in human and animal models [7-10].

In humans, the dose of epidural dexmedetomidine reported is in the range of 1.5-2 µg/kg. *Fukushima et al.* [8] administered 2 µg/kg epidural dexmedetomidine for post-operative analgesia in humans without any reports of neurological deficits.

Also, *Maroof et al.* [9] used epidural dexmedetomidine, approximately 1.5 µg/kg, to decrease the incidence of post-operative shivering without any reports
of neurological deficits.

In a study for the effect of low-dose intrathecal dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block in patients undergoing transurethral resection of prostate or bladder tumor under spinal anesthesia [10], it was concluded that: dexmedetomidine (3 microg) or clonidine (30 microg), when added to intrathecal bupivacaine, produces a similar prolongation in the duration of the motor and sensory block with preserved hemodynamic stability and lack of sedation.

Clonidine, the α_2-adrenoceptor agonist, produces analgesia without significant respiratory depression after systemic, epidural, or intrathecal administration. [11] Clonidine's analgesic effect is more pronounced after neuraxial injection, which suggests a spinal site of action and makes this route of administration preferable. The addition of clonidine also prolongs the duration of action of bupivacaine after intrathecal and epidural administration in adults. [11]

This α_2- agonist is devoid of opioid side effects but may produce excessive sedation, hypotension and bradycardia in adults. In children, addition of clonidine to local anaesthetics prolongs the duration of postoperative analgesia after inguinal hernia repair and minor orthopaedic surgery. [12]

Fentanyl, a lipophilic opioid, is added frequently to local anaesthetics in children, but its beneficial effects are debated. Side effects, such as nausea,vomiting or respiratory depression, are not uncommon. [13]

Tramadol is a centrally acting analgesic which has been licensed for use in children older than 1 yr of age in many of European countries since 1977. [14]

Tramadol has been shown to provide effective, long-lasting analgesia after epidural administration in both adults and children. It acts at opioid receptors and also appears to modify transmission of pain impulses by inhibition of monoamines reuptake.

Tramadol is a racemic mixture of two enantiomers. The (+) enantiomer has a moderate affinity for the opioid μ receptor, greater than that of the (-) enantiomer. In addition, the (+) enantiomer inhibits serotonin reuptake and the (-) enantiomer is a norepinephrine reuptake inhibitor. These complementary properties result in a synergistic antinociceptive interaction between the two enantiomers. The result is an opioid with a striking lack of respiratory depressant effect despite an analgesic potency approximately equal to that of pethidine. [15] In addition, biotransformation of tramadol in the liver results in many phase I and II metabolites. Of all the metabolites, O-demethyl tramadol (M1) is the only active metabolite with a greater affinity for the μ receptor than the parent compound. [15]

However, there are no comparative data on the effect of caudal administration of dexmedetomidine, clonidine, tramadol, or fentanyl on the duration of effective surgical analgesia in children.

Aim of the work:

The aim of this randomized, prospective clinical study was to investigate and compare the effect of addition of dexmedetomidine, clonidine, tramadol, or fentanyl to local anesthetics for caudal analgesia in children, and to evaluate if these additives prolonged the duration of surgical analgesia,

thus allowing single shot caudal analgesia to be recommended for surgery lasting more than 90 min.

Materials and Methods:

The study was performed at Anesthesiology Department, Faculty of Medicine, Elfayoum University, approved by the Hospital Ethics Committee, and written parental informed consent was obtained.

Patients:

This study included 100 healthy male and female children, ASA I and II,
Aged 3–10yr, and their body weight between 10 –30kg, undergoing elective surgical procedures expected to last more than 90 min, and scheduled to receive general anesthesia combined with caudal extradural block. A sensory block up to T10 is sufficient for all these surgical procedures.**Exclusion criteria** were: contraindications to caudal anesthesia, and ASA III or greater.

Methods:

All children received standard premedication 30–40 min before surgery in the form of midazolam 0.2 mg/kg orally.

Anesthesia was induced by face mask with halothane and 60% nitrous oxide in oxygen. After placement of an i.v. cannula, the trachea was intubated without the use of a neuromuscular blocking agent and the lungs were ventilated by assisted manual ventilation until regular spontaneous breathing was achieved. Anesthesia was maintained with isoflurane (0.6 MAC corrected for age), using standard monitoring.   Caudal anesthesia was performed with a 22-gauge needle under complete aseptic conditions using Betadine then Alcohol, with the child in a left lateral position and immediately turned supine after injection of the drug, and a glucose/saline solution was infused i.v. at the rate of 10 mL / kg/ h.

Children were allocated randomly in one of five treatment groups for caudal block (n=20) by opening a sealed envelope, and one of the five different mixtures described below was administered on a weight-related basis into the caudal space.

The five groups were as follow:

 I: Group B: received 1 ml/ kg of a mixture of equal parts of 0.25% bupivacaine,
                And 1% lidocaine (Maximum dose 20 ml), with normal saline
                (The same volume as that required for additives in the other groups);

II: Group C: received the same mixture of local anesthetics in addition to
                Dexmedetomidine 1.5µg/ kg. *(Precedex, 100µg/ml; Abbott Laboratories).*

III: Group C: received the same mixture of local anesthetics in addition to
                Clonidine 2µg/ kg. *(Catapres, 150µg/ml; Boehringer Ingelheim, U.K).*

IV: Group T: received the same mixture of local anesthetics in addition to
                Tramadol 2mg/ kg. *(Minapharm; Grünenthal, Germany)*

V: Group F: received the same mixture of local anesthetics in addition to

Fentanyl 2µg/ kg *(Fentanyl- Janssen Pharmaceutica, N.V. Belgium)*.

No other perioperative analgesia was given.

For all patients, the study period was classified into tow parts; intraoperative part (in the operating room) for three hours starting from caudal injection, and postoperative part in the post anesthesia care unite (PACU) for the next three hours.

Intraoperative monitoring:

Oximetry was monitored continuously and **oxygen desaturation** was defined as SpO_2 <95% that required supplemental oxygen via a mask.

Heart rate (HR), and systolic arterial pressure (SAP) values were recorded using a non-invasive automated oscillometric device 5 min before the induction of anesthesia (baseline value; 30–45 min after oral sedation), after induction but before caudal anesthesia, and then every 5 min after caudal anesthesia during operation, and after the end of operation and recovery till the end of 3h after caudal injection.

During surgery, **adequate analgesia** was defined by haemodynamic stability, as indicated by the absence of an increase in HR or SAP of more than 15% compared with baseline values obtained just before the surgical incision, with isoflurane concentration maintained at approximately 0.6 MAC. An increase in HR or SAP within 15 min of skin incision indicated failure of caudal anesthesia.

 If, more than 90 min after skin incision, HR or SAP increased by more than 15%, analgesia was considered inadequate and children received rescue opioid during operation (Fentanyl 1µg/ kg). The need for rescue opioid was considered as the first end-point of the study and subsequent data obtained from those children were no longer considered.

Patients breathed spontaneously with manual assistance throughout the anesthetic and the surgical procedure. Anesthesia was discontinued when the wound dressing had been applied; and the patient's trachea was extubated, then, all patients were monitored in the operating room till the end of 3h after caudal injection, then transfered to PACU breathing room air.

Time from caudal block to skin incision, time from caudal block to the end of surgery, and time from discontinuing the volatile anesthetic to tracheal extubation were recorded in every case.

In the PACU;

Glucose/saline solution was infused i.v. at the rate of 4mL/kg/h. Oximetry was monitored continuously as intraoperatively and monitoring of hemodynamic state (SAP and HR), with assessment of analgesia, sedation, and development of any side effects until 6 h after caudal block. Observations were performed by a PACU nurse blinded to the analgesic used.

Bradycardia, defined as a 20% decrease in HR compared with preoperative values, was treated with atropine 0.01 mg/kg i.v.

Hypotension, defined as a 20% decrease in SAP compared with preoperative values, was treated with rapid infusion of fluids or, if that was unsuccessful, with the use ephedrine 5 mg i.v as appropriate.

Analgesia assessments were made every 30 min in PACU by an **Observational Pain/discomfort Scale (OPS)** to assess *five behavioral objective variables*: (crying, facial expression, position of torso, position of legs, motor restlessness). Each variable was scored 1–3 (1 = none, 2 =

moderate, 3 = severe) to give a cumulative score of 5–15 with which to qualify analgesia (e.g., 5 = excellent,
15 = ineffective). If the OPS score was >11 in two subsequent measurements or if the patient showed obvious signs of pain, they were given supplementary analgesics in the form of 15 mg/kg rectal paracetamol. Residual pains were reassessed 30 min later and fentanyl 1μg/ kg i.v. was administered if pain scores remained unchanged.

Times to administration of paracetamol and fentanyl were recorded. The time from caudal block to the first postoperative analgesic administration (paracetamol) was the end-point of the study (Duration of analgesia).

Duration of analgesia was defined as the time from caudal injection to the first request for supplementary analgesics. If no rectal paracetamol was necessary within the 6-h observation period (after caudal injection), the duration of analgesia was counted as 360 min.

Sedation score was assessed every 30 min on a four-point ***Patient Sedation Score (PSS)***, which was assigned as follows: 1 = asleep, not arousable by verbal contact; 2 = asleep, arousable by verbal contact; 3 = drowsy/not sleeping; 4 = alert/aware. The PSS was used to quantify sedation and to help to identify side effects, such as respiratory depression from excess sedation.

The times from caudal injection to first supported standing and first spontaneous voiding after anesthesia were also documented. Patients were discharged from the PACU to the ward 6 h after caudal injection.

Statistical analysis:

Before the study, the number of patients required in each group was determined after a power calculation according to data obtained from previous studies. It was assumed that duration of surgical analgesia with a mixture of local anesthetics was 90 min (range 60–120 min), and that addition of fentanyl would increase this time by 50%, and clonidine by 100%, as demonstrated for postoperative analgesia. According to this hypothesis, a sample size of 20 patients in each group was adequate.

All data are expressed as mean ± standard deviation (SD). Statistical comparisons among the four groups were performed by using a two-way analysis of variance (ANOVA) to compare changes within each group, and paired Student's t-test to compare different group data. Time to the first request for supplementary analgesics, time to first micturition and time to first spontaneous standing were compared using ANOVA followed by the Neuman-Keuls test if differences between groups were found.Significance was determined at (P < 0.05).

Results:

112 children included in the study but twelve children did not complete it because of failure of the caudal block (subcutaneous injection) in seven patients, and insufficient duration of the surgical procedure (80 min) in five patient.

As regards the demographic characteristics, there were no differences in the mean age, height, or weight of patients, sex distribution, and ASA physical status, time from caudal block to surgical incision, duration of surgery, time from end of surgery to extubation and duration of general anaesthesia and among the five groups as seen in Table (1).

Table (1): Demographic data of all groups (mean ± SD):

	Group B	Group D	Group C	Group T	Group F
Age (yr).	6.1±1.8	6.2±2.2	6.5±2.3	6.3±2.1	6.2±2.7
Sex (Male/Female).	9/11	10/10	9/11	10/10	11/9
Body weight (kg).	20.7±	21.5±	21.9±5.6	20.8±	21.4±
ASA class I/II.	4.4	5.2	17/3	5.3	6.4
Surgery (number of patients):	18/2	17/3		18/2	19/1
			11		
Hypospadias surgery.	12	10	6	13	10
Inguinal herniotomy.	5	6	3	5	7
Orthopedic surgery.	3	4		2	3
Time from caudal block to			24±9		
Surgical incision (min).	25±13	23±11	141±6	22±14	23±13
Duration of operation (min).	140±9	139±10	9±8	138±11	140±8
Time to extubation (min).	11± 4	10±6	153±8	10±4	11±2
Duration of G.A. (min).	155±6	151±9		150±10	153±7

No significant difference between the five groups.   n = 20 patients in each group.
 G.A.; General anesthesia.
Group B; 1 ml/ kg of a mixture of equal parts of 0.25% bupivacaine, and 1% lidocaine
        (Maximum dose 20 ml), with normal saline
         (The same volume as that required for Additives in the other groups);
Group D; the same mixture of local anesthetics in addition to Dexmedetomidine 1.5µg/ kg.
Group C; the same mixture of local anesthetics in addition to Clonidine 2 µg / kg.
Group T; the same mixture of local anesthetics in addition to Tramadol 2mg/ kg.
Group F; the same mixture of local anesthetics in addition to Fentanyl 2µg/ kg.

Hemodynamic Stability:

Baseline HR and SAP recorded before induction of general anesthesia were similar in the five groups Tables (2and 3). Compared with baseline values, HR and SAP decreased in all groups by 10–15% during anesthesia, and increased by 5–15% during recovery. There were no significant differences in HR and SAP profiles between the five groups.

Table (2): Heart rate changes during study period in all groups (mean ± SD):

Group	Baseline	After G.A.	5min After C.A.	15min	30min	1hour	2hours	3hours	4hours	5hours	6hours
Group B	108.24± 12.67	98.41± 13.53	107.54± 19.35	108.44± 16.67	112.74± 18.68	115.42± 19.47	111.84± 16.63	112.44± 15.81	117.56± 12.69	109.44± 12.72	108.44± 11.87
Group D	113.44± 10.37	101.24± 12.61	108.44± 15.67	110.17± 10.63	111.33± 12.46	112.13± 11.67	108.34± 12.54	110.44± 11.61	111.24± 10.37	109.34± 12.55	108.47± 12.57
Group C	111.64± 12.62	99.74± 13.57	102.44± 12.47	104.34± 12.33	102.64± 14.47	101.24± 13.77	103.47± 12.67	108.46± 15.88	108.14± 12.68	108.52± 13.44	105.44± 12.33
Group T	115.24± 10.61	100.44± 8.67	108.24± 10.63	110.44± 11.67	107.74± 12.62	108.84± 12.27	104.84± 14.61	109.44± 14.67	108.54± 12.37	118.44± 11.67	104.64± 12.17
Group F	110.64± 12.61	102.77± 11.69	106.42± 12.67	108.44± 12.68	102.66± 12.32	105.48± 12.39	108.23± 13.26	115.77± 12.99	107.64± 12.13	116.22± 12.54	108.22± 12.43

No significant difference between the five groups.   n = 20 patients in each group.
 Baseline; 5min before general anesthesia.
 After G.A; after general anesthesia but before caudal anesthesia. C.A.; caudal anesthesia.
Group B; 1 ml/ kg of a mixture of equal parts of 0.25% bupivacaine, and 1% lidocaine
        (Maximum dose 20 ml), with normal saline

(The same volume as that required for Additives in the other groups);
Group D; the same mixture of local anesthetics in addition to Dexmedetomidine 1.5µg/ kg.
Group C; the same mixture of local anesthetics in addition to Clonidine 2 µg / kg.
Group T; the same mixture of local anesthetics in addition to Tramadol 2mg/ kg.
Group F; the same mixture of local anesthetics in addition to Fentanyl 2µg/ kg.

Table (3): Systolic pressure changes during study period in all groups (mean ± SD):

Group	Baseline	After G.A.	5min After C.A.	15min	30min	1hour	2hours	3hours	4hours	5hours	6hours
Group B	106.12± 11.56	97.41± 12.53	105.54± 15.35	101.44± 14.67	108.74± 13.68	110.42± 17.47	109.84± 15.63	101.44± 14.81	109.56± 12.69	98.44± 12.72	89.44± 14.87
Group D	110.44± 10.37	96.24± 12.61	103.44± 15.67	100.17± 10.63	108.33± 11.46	107.13± 10.67	108.34± 12.54	101.44± 11.61	98.24± 10.37	100.34± 12.55	95.47± 12.57
Group C	109.64± 12.62	99.74± 13.57	102.44± 12.47	104.34± 12.33	106.64± 13.47	103.24± 13.77	105.47± 12.67	101.46± 13.88	100.14± 12.68	101.52± 13.44	97.44± 12.33
Group T	105.23± 10.61	100.44± 8.67	106.24± 10.63	103.44± 10.57	102.74± 12.62	100.84± 12.17	102.84± 13.61	100.44± 14.67	97.54± 12.37	109.44± 11.67	107.64± 12.17
Group F	107.64± 12.61	102.77± 11.69	100.42± 12.67	101.44± 12.68	103.66± 12.32	105.48± 12.39	107.23± 13.26	104.77± 12.99	100.64± 12.13	105.22± 12.54	108.22± 12.43

No significant difference between the five groups.   n = 20 patients in each group.
Baseline; 5min before general anesthesia.
After G.A; after general anesthesia but before caudal anesthesia. C.A.; caudal anesthesia.
Group B; 1 ml/ kg of a mixture of equal parts of 0.25% bupivacaine, and 1% lidocaine
(Maximum dose 20 ml), with normal saline
(The same volume as that required for Additives in the other groups);
Group D; the same mixture of local anesthetics in addition to Dexmedetomidine 1.5µg/ kg.
Group C; the same mixture of local anesthetics in addition to Clonidine 2 µg / kg.
Group T; the same mixture of local anesthetics in addition to Tramadol 2mg/ kg.
Group F; the same mixture of local anesthetics in addition to Fentanyl 2µg/ kg.

Analgesia and Sedation:
Intraoperative analgesia:
The mean duration of surgery was 140min in the five groups. Successful single shot caudal block provided adequate surgical analgesia in all children in the five groups as observed by hemodynamic stability during intraoperative study periods Tables (2and 3) . No intraoperative analgesic supplements were needed.
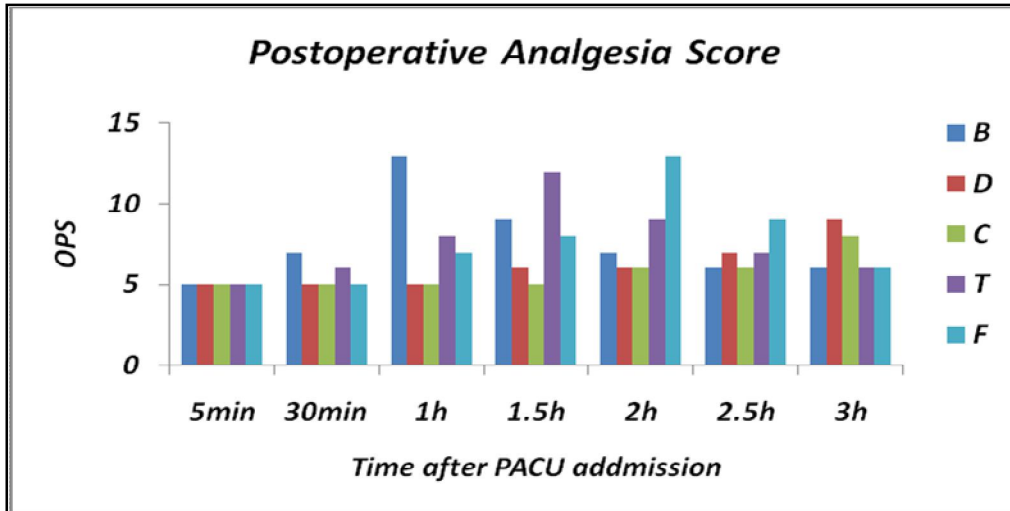### Postoperative analgesia and Sedation:
All children were sufficiently awake within 15 min and were brought to the PACU breathing room air. Monitoring of hemodynamic state (HR and SAP) Tables (2and 3), with assessment of analgesia and sedation revealed that there was a tendency for earlier analgesic requirements in group B Figures (1and 2).
Mean duration of analgesia (defined as the time from caudal injection to the first request for supplementary analgesics after operation) was significantly longer in the four groups who received additives compared with control group: (245 ± 10) min in group B, (347 ± 13) min in group D, (350 ± 10) min in group C, (280 ± 20) min in group T, and (275 ± 15) min in group F ($P < 0.05$).
In groups D and C, the mean duration of analgesia was significantly longer than groups T and F ($P < 0.05$) , but no significant differences were observed between groups D and C.

Sedation scores were higher in groups D and C, and most of children in these two groups were alert earlier than other groups without request for supplementary analgesics, although the differences were not statistically

significant Figure (2).

Figure (1): Postoperative Analgesia Score in All Study Groups.
OPS = Observational Pain/discomfort Scale,
B = Bupivacaine, D = Dexmedetomidine, C = Clonidine, T = Tramadol, F = Fentanyl.
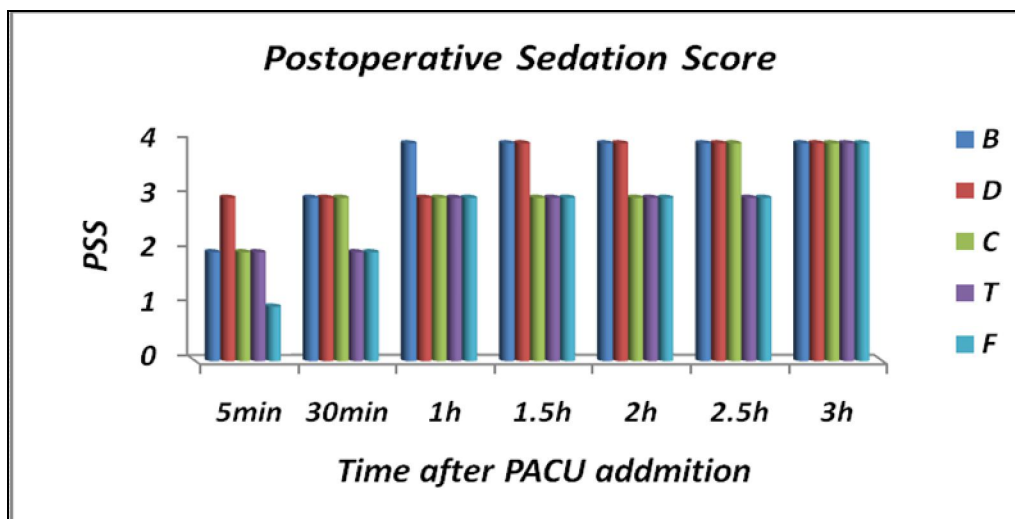

Figure (2): Postoperative Sedation Score in All Study Groups.
PSS = Patient Sedation Scores (1 = asleep, not arousable by verbal contact; 2 = asleep, arousable by verbal contact; 3 = drowsy/not sleeping; 4 = alert/aware)
B = Bupivacaine, D = Dexmedetomidine, C = Clonidine, T = Tramadol, F = Fentanyl.

SIDE EFFECTS

Neuraxial clonidine prolongs motor blockade of local anesthetics and can delay recovery of bladder function. However, in this study all patients could move their legs at the end of the six-hour observation period in the hospital.

The times to first supported standing with complete regression of motor block and spontaneous voiding were similler among all groups, and no patient required bladder catheterization. Also, ephedrine was not needed in either group. Five patients in group D and seven patients in group C required atropine ($P < 0.05$).

A transient respiratory depression, with decrease in oxygen saturation to 92% was observed within the first hour of recovery in two children who received fentanyl; but otherwise, all patients had peripheral oxygen saturation greater than 96% at all times and did not require additional oxygen in the PACU.

Vomiting was observed in the PACU only in four children in group F, and in three children in group T ($P < 0.05$). The 2-week follow-up questionnaire did not show any new onset 'of back, buttock or leg pain or paresthesia in all study groups.

Discussion:

The use of intrathecal or epidural clonidine has a well-established synergistic effect with local anesthetics [11-12]. Most of the clinical experience gained in the use of intrathecal or epidural α_2-adrenoceptor agonists has been described with clonidine.

Studies using a combination of intrathecal or epidural dexmedetomidine and local anesthetics are lacking. Analgesic properties were found when intrathecal or epidural dexmedetomidine was used in animal models. [7-11] Animal studies conducted in rats, rabbits, dogs and sheep have used intrathecal dexmedetomidine at a dose range of 2.5-100 µg. [7] The largest dose of intrathecal dexmedetomidine, 100 µg, was used in a sheep model, where a 7-day follow-up showed no neurological deficits in the studied animals. [11]

In humans, the dose of epidural dexmedetomidine reported is in the range of 1.5-2 µg/kg. *Fukushima et al.* [8] administered 2 µg/kg epidural dexmedetomidine for post-operative analgesia, and *Maroof et al.* [9] used epidural dexmedetomidine, approximately 1.5 µg /kg, to decrease the incidence of post-operative shivering without any reports of neurological deficits. Intrathecally administered α_2-agonists have a dose-dependent sedative effect [16]. Moreover, in the study of *Kanazi et al.* [10] the 2-week follow-up questionnaire showed that intrathecal dexmedetomidine at a dose of 3 µg, was not associated with any new onset of back, buttock or leg pain, or weakness.

In this study, a safe dose of dexmedetomidine (1.5µg/ kg) and clonidine (2µg/ kg) was selected based on previous human studies [8, 9, and 12].

The mechanisms by which intrathecal α_2-adrenoceptor agonists prolong the motor and sensory block of local anesthetics is not well understood. [10] It may be an additive or synergistic effect secondary to the different mechanisms of action of the local anesthetic and the α_2-adrenoceptor agonist. The local anesthetic acts by blocking sodium channels, whereas the α_2-adrenoceptor agonist acts by binding to pre-synaptic C- fibers and post-synaptic dorsal horn neurons. Intrathecal α_2-adrenoceptor agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons. [11] This

antinociceptive effect may explain the prolongation of the sensory block when added to spinal anesthetics.

The results of this study showed that for caudal blockade, the addition of dexmedetomidine (1.5μg/ kg) or clonidine (2μg/ kg) to 0.25% bupivacaine significantly prolongs the duration of analgesia (347 ± 13) min in group D, (350 ± 10) min in group C, vs (245 ± 10) min in group B), and reduces the postoperative analgesic requirements compared with bupivacaine alone with minimal side effects.The differences between the dexmedetomidine and clonidine groups was not statistically significant.

These findings confirm previous studies[17] in which a mixture of 0.25% bupivacaine 1 mL/kg and clonidine 2 μg/kg produced a longer duration of caudal analgesia in children than bupivacaine alone (9.8 vs 5.2 hours, respectively)

Optimal extradural doses of clonidine are not well determined. In children, doses of 1 μg/kg , 2 μg/kg or 3 μg/kg have been used without adverse respiratory or hemodynamic effects, while a decrease in SAP and HR was observed after a dose of 5 μg kg-1. However, hypotension is a rare complication in infants and children less than seven years of age. [12] Because cardiac output in younger children and infants depends on HR, a major concern of this study was hemodynamic safety.

Clonidine inhibits sympathetic preganglionic neurons; therefore, the degree of clonidine-induced hypotension is also related to the spinal site of injection. Thoracic epidural administration of clonidine closer to the origin of sympathetic neurons causes a more pronounced MAP decrease than lumbar clonidine administration. Thus, a more distant caudal site of injection might favor a moderate hemodynamic response to clonidine [18].

 In this study, although sedation was not significantly different among the study groups, it was slightly more pronounced in the D and C groups. However, because sedation made the children look more comfortable, it was actually appreciated by parents and ward staff, and was not regarded as an adverse side effect.

Fentanyl is added commonly to local anesthetics in the extradural space to improve analgesia in the postoperative period. However, few studies have addressed the benefit of fentanyl for single shot procedures. The addition of fentanyl produced only a slight change in the quality and duration of analgesia after administration of 2% lidocaine with epinephrine for a short surgical procedure or after administration of 0.125% bupivacaine. Therefore, it was concluded that addition of fentanyl to local anesthetics offered no advantage over administration of local anesthetics alone for short surgical procedures in children [14].

Another study [18] concluded that addition of clonidine or fentanyl to local anesthetics prolonged the duration of surgical analgesia of caudal block, allowing single shot caudal anesthesia to be recommended for surgery lasting 90–150 minutes. Clonidine had some advantages over fentanyl as it did not produce clinically significant side effects.

 In this study, fentanyl 2μg / kg, when injected into the caudal extradural space, produced useful analgesia for up to 4.5h. However, the addition of fentanyl to local anesthetics increased significantly the incidence of vomiting compared with other groups who did not receive fentanyl. The emetic effect of extradural opioid is well known and involves supraspinal

mechanisms, while clonidine exhibits antiemetic properties when administered by the oral or i.v. route [14].

Also in this study, tramadol 2mg/ kg, when injected into the caudal extradural space, produced useful analgesia for up to 5h, and the mean duration of surgery was 140min. In other studies, caudal tramadol produced useful analgesia for up to 12h without a significant incidence of side effects. [20]. However, if the period of time between performing the caudal injection and recovery of the child from anesthesia was <2 h, the incidence of immediate pain (requiring rescue analgesia) was high (30%), demonstrating a slow onset of action of caudal tramadol.But, if the operation was longer, then caudal tramadol produced good quality analgesia for an average of 10.7 h [19]. The slow onset time of caudal tramadol may imply that there is little advantage in injecting tramadol into the extradural space and that i.v. administration may be equally efficacious.As an adjunct to bupivacaine, tramadol may prove more useful in young children and infants than other opioids because of its lack of respiratory depressant effects [20].

Conclusions:

It was concluded that for caudal blockade, the addition of dexmedetomidine 1.5μg/ kg, or clonidine 2μg/kg, or tramadol 2mg/ kg, or fentanyl 2μg/ kg to 0.25% bupivacaine significantly prolongs the duration of analgesia, thus allowing single shot caudal anesthesia to be recommended for surgery lasting 90–150 min, and reduces the postoperative analgesic requirements compared with 1 ml/ kg of a mixture of equal parts of 0.25% bupivacaine and 1% lidocaine. This could be a safe and cheap alternative to extradural catheter placement for surgical procedures of intermediate duration.Dexmedetomidine and clonidine have an equipotent effect on the characteristics of the block without any significant hemodynamic instability or sedation.Also, dexmedetomidine and clonidine have some advantages over fentanyl, as both of them did not produce clinically significant side effects. Undesirable side effects such as vomiting and transient oxygen desaturation were observed only in children who received extradural fentanyl. Therefore, dexmedetomidine or clonidine may be the drugs of choice to prolong duration of caudal anesthesia provided by a single injection in children.

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