



Comparison between different anaesthesia techniques for protecting renal function in children undergoing radical nephrectomy

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ABSTRACT

Background: Although no standard paradigm has been approved yet superior than other in prevention of deterioration of renal function in children after radical nephrectomy (RN), early recognition of acute kidney injury (AKI) is a cornerstone. Cystatin C and neutrophil gelatinase-associated lipoprotein (NGAL) has shown to exhibit renal tubular stress earlier than ordinary biomarkers. The aim of the study was to compare between different anaesthesia techniques in protecting renal function in children undergoing RN.

Patients and methods: 75 children (5–10 years) scheduled for RN were randomly categorized to: Dexmedetomidine (D) group, where DEX. 0.8 µg/kg was infused over 10 min as a loading dose, and then continued at a rate 0.4 µg/kg/h. Caudal (C) group, where 1 mL/kg dose of 0.25% bupivacaine was given and Placebo (P) group, where normal saline was given. Serum creatinine, creatinine clearance, Cystatin C and NGAL were assessed after induction of anaesthesia, 12 and 24 h postoperatively.

Results: Cystatin C and NGAL values decreased significantly in group D relative to group C and group P at all times of measurement. Urine output was significantly higher in the Dex. group. Serum creatinine and creatinine clearance showed no significant difference between the three studied groups at all times of measured. Dex members were more sedated and had lower objective pain scores relative to the other two groups.

Conclusions: Dexmedetomidine showed promising power in attenuation of renal stress and prevention of AKI in children undergoing RN when using cystatin C and NGAL biomarkers into clinical prediction schemes.

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1. Introduction

Uptodate, renal cell carcinomas (RCC) are one of the prevalent primary renal neoplasms affecting children and surgical RN is the conventional standard of care, as the choice of non-surgical modalities like irradiation and hormono-chemotherapy is still a subject of debate [1,2].

Worsening of postoperative renal function is not so far from these patients who underwent nephrectomy for RCC, thus perioperative preservation of renal function is a great challenge facing anaesthologist aiming to abolishment of postoperative acute kidney injury (AKI) development [3]. AKI is a serious clinical diverse which increases morbidity and mortality thus enhancing the risk of development of chronic kidney disease (CKD). Several studies had reported the associations between AKI and CKD after radical nephrectomy is as high as 65% [4,5].

For years, the diagnosis of AKI was based on ordinary kidney function tests like serum creatinine and blood urea nitrogen, which are not efficient nowadays, as they lack specificity for renal damage, besides they are affected by many other factors apart from kidney injury [6–9].

Cystatin C is an endogenous protein with low molecular weight (13 k Da), that is freely filtered at the glomeruli and completely reabsorbed in the proximal renal tubules. It indicates renal injury indirectly through decreased glomerular filtration rate GFR [10,11]. Serum neutrophil gelatinase-associated lipocalin (NGAL) is a promising glycoprotein produced by neutrophils and epithelial cells of the proximal convoluted tubule of the nephron cells. After renal stress or nephrotoxic damage its peak plasma level is reached within 6 h, then remains sustained for as long as 5 days [12–14].

Dexmedetomidine (Dex.) a short acting, highly selective alpha-2 agonist, that possess potent analgesic, amnestic, hypnotic and sedative properties via actions on sleep-awake cycle in the brain. Several evidences reported its possible ability for renal protection [15–18].

Caudal epidural blockade is well-known efficient technique that offer postoperative analgesia for multiple surgical procedures in children. Beside hemodynamic stability, they prevent progression of acute postoperative pain to chronic pain [19,20].

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We hypothesized that uses of Dex infusion in a programmed fashion in children undergoing RN, could produce optimum preservation of kidney function from the concurrent perioperative insult even in a very early phase of renal stress, relative to ordinary used protocols.

2. AIM of the study

The primary outcome was comparison between effect of different anaesthesia techniques on preservation of kidney function using early predictors cystatin C and NGAL. Secondary outcomes included monitoring kidney function using ordinary measurements like serum creatinine and creatinine clearance, in addition to postoperative pain assessment, and sedation score.

3. Patients and methods

After approval of the Ethical committee of faculty of Medicine, Alexandria University and obtaining an informed written consent from parents of the children included in the study, 75 patients with the American Society of Anesthesiologists (ASA) physical status I–II, aged 5–10 years sex, undergoing elective RN were randomly enrolled using closed envelope method. The study was registered in Clinical Trials. gov (NCT05271253).

The patients were excluded if they were on current treatment with α_2 agonists, had renal impairment (creatinine clearance < 90 ml/min), there was persistent intraoperative hypotension [mean arterial blood pressure < 65 for > 20 min] or the use of intraoperative diuretics for treatment of oliguria. Also, those with bleeding and coagulation disorders, congenital heart diseases and skin lesion at puncture site.

Patients were randomly allocated into three equal groups (25 patients each): Dexmedetomidine (D) group, where Dex. (Precedex, hospira, Inc., Lacke Forest, USA) 0.8 $\mu\text{g}/\text{kg}$ was given intravenously over 10 min as a loading dose, and then infused at a rate of 0.4 $\mu\text{g}/\text{kg}/\text{h}$. Group (C): caudal group, where caudal anaesthesia was given using 1 mL/kg dose of 0.25% bupivacaine without epinephrine and Placebo (P) group, where normal saline instead of Dex. infusion was given in a volume (ml) and rate (ml/h) calculated according to the patient's body weight.

All children were assessed thoroughly preoperatively by history taking, physical examination and laboratory investigations (complete blood count, coagulation profile, liver function and kidney functions.)

24 hours before surgery, base line values of serum creatinine (blood sample), creatinine clearance (24 h urine sample collection) were obtained using standard laboratory methods. Also, base line values of serum cystatin C and serum NGAL were obtained using commercially available kits (Roche Diagnostics, Mannheim,

Germany) and (Biosite Incorporated, San Diego, CA, USA), respectively, by ELISA method. Establishment of method and degree of sample dilution were carried out prior to analysis according to manufacture instruction.

All children were instructed to void just before admission to the operating room.

In the operating theater, all patients were monitored throughout surgery by continuous electrocardiography, heart rate, pulse oximetry, non invasive blood pressure, and end-tidal capnography by (Datex-Omeda model S/5) monitor. Induction was carried out with fentanyl (1–1.5 $\mu\text{g}/\text{kg}$), and propofol (1–2 mg/kg). For facilitating endotracheal intubation, atracurium was administered at an initial dose of 0.5 mg/kg followed by boluses of 0.03 mg/kg every 20–40 min. Under aseptic technique, an arterial line, central venous catheter and Foley catheter were inserted. Anaesthesia was maintained using isoflurane 1–2% with 50% oxygen in air, and patients were mechanically ventilated to maintain the end-tidal CO_2 tension between 35 and 40 mm Hg and an oxygen saturation of 98%. Fentanyl and atracurium increments were given as required.

In group (D) Dex.infusion 0.8 $\mu\text{g}/\text{kg}$ was given intravenously over 10 min as a loading dose, and then infused at a rate of 0.4 $\mu\text{g}/\text{kg}/\text{h}$. In group (P) normal saline was given in a volume (ml) and rate (ml/h) calculated according to the patient's body weight. Both Dex.infusion and normal saline were prepared by independent participant and were started immediately after induction of anaesthesia and continued for the first 24 h postoperatively. In group (C) patients were placed in the left lateral position and caudal anaesthesia was given (1 mL/kg dose of 0.25% bupivacaine without epinephrine) using loss of resistance technique.

All patients in all groups received a strict fluid replacement according to the standard fluid replacement administration guidelines during anaesthesia. At the end of surgery, patients were turned to supine position, oral secretion was aspirated then anaesthesia was discontinued and 100% oxygen was administered. Muscle relaxants were reversed by neostigmine 0.04–0.08 mg/kg and atropine 0.02 mg/kg, and then the patients were extubated fully awake after return of protective airway reflexes and full muscle power. All patients were monitored in the ICU for 24 h after surgery. Serum creatinine, creatinine clearance, Cystatin C and NGAL was assessed 24 h before surgery, after induction of anaesthesia, 12 and 24 h postoperatively. Urine output was assessed intraoperatively every 1 h and postoperatively every 6 h for the first 24 h. Sedation was assessed during the first 5, 15, 30, and 60 mins using a five-point sedation scale [21]. Sedation level: alert = 0, occasionally drowsy = 1, drowsy and easy to arouse = 2,

somnolent and difficult to arouse = 3, unarousable = 4. Postoperative pain was assessed using the objective pain score (OPS) [22] at the following time points: immediately on arrival to ICU, 2, 4, 8, 12, 16 and 24 h post-operatively.

OPS is based on five parameters:

- Blood pressure (within 10% of preoperative level = 0, > 20% = 1, > 30% = 2).
- Crying (not crying = 0, crying but respond to tender loving care = 1, crying not responding to tender loving care = 2).
- Movement (none = 0, restless = 1, thrashing = 2).
- Agitation (asleep or calm = 0, mild = 1, hysterical = 2).
- Complains of pain (asleep, no pain = 0, cannot localize = 1, localize = 2).

Each parameter of OPS was given a score of 0–2, with 2 being the worst, making the worst possible score of 10. Postoperative analgesia in the form of intravenous Paracetamol 15 mg/kg was given if the patients experienced pain (OPS \geq 5). Fentanyl 1 μ g/kg was the second rescue analgesic if OPS were \geq 3 in spite of I.V paracetamol. The total amounts of intraoperative fentanyl consumed, as well as the total amount of postoperative paracetamol consumption, in each group were recorded.

Oliguria was defined as urine output < 0.5 ml/kg/h. After exclusion of catheter obstruction, patients were managed with good hydration. If it persists, 10 mg I.v Lasix was given that could be repeated twice. If no response, nephrology consultation was ordered. Hypotension was defined as systolic arterial pressure < (70 mm Hg + 2 x age in years) requiring fluid bolus administration. Bradycardia was defined as HR < 60 beats/min requiring atropine administration.

4. Statistical analysis

Sample size calculation was based on previous study evaluating the effects of prophylactic dexmedetomidine administration on postoperative acute kidney injury (AKI) in pediatric patients undergoing cardiac surgery [23]. Accordingly, a sample size of 25 per study group was estimated to achieve at least an 80% power ($\alpha = 0.05$) to detect a difference of at least 30%.

Data were fed to the computer and analysed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Description of quantitative (numerical) data was performed in the form of mean + SD. Description of qualitative data (categorical) was performed in the form of number of cases and percent (Fisher's exact X^2 test was used whenever possible). Analysis of unpaired numerical variable was performed using analysis of variance (ANOVA) and unpaired student t-test. The significance level was set at P-value of 0.05 or less and P-value of 0.01 or less was considered highly significant.

5. Results

79 participants were enrolled in the study, four of which were dropped from the study as they were treated with diuretics. The remaining 75 participant were randomly allocated into three equal groups (Figure 1).

Patients' characteristics regarding age, sex, and body weight were comparable in the three studied groups ($p > 0.05$).

Monitoring kidney function using ordinary measurements like serum creatinine and creatinine clearance, showed no statistically significant difference between the three studied groups at all times of measurements ($p > 0.05$) (Table 1).

However cystatin C, preoperative baseline values of the three studied groups were similar ($p = 0.09$) (Table 2). After that, it decreased significantly in the Dex. group ($p < 0.05$) relative to the other two groups at all times of further measurement with no significant difference between group C and group P (Table 2).

Moreover, regarding serum NGAL, preoperative baseline values of the three studied groups were similar ($p > 0.05$) (Table 2). After that, it increased significantly in group C and group P relative to group D at all times of further measurement (Table 2).

Correlation between evaluation of the kidney function using ordinary markers (serum creatinine and creatinine clearance), with the new predictors (serum cystatin C and NGAL) in the three groups revealed a negative significant correlation in the Dex. group ($r = -0.078$, $p = 0.001$) relative to non-Dex. groups which revealed no correlation.

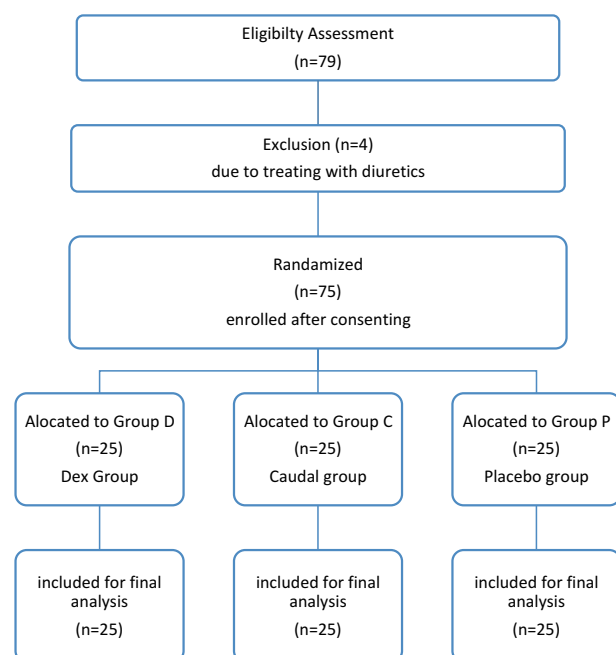


Figure 1. Study flow chart.

Table 1. Comparison between the serum creatinine and creatinine clearness in the three studied groups at different periods of follow up (Mean ± S.D).

	Baseline (Preoperative)	After Induction	12 h post-operative	24 h post-operative
Serum Creatinine				
Group C Mean ± S.D	0.793 ± 0.161	0.795 ± 0.149	0.792 ± 0.137	0.791 ± 0.136
Group D Mean ± S.D	0.793 ± 0.135	0.797 ± 0.131	0.794 ± 0.121	0.782 ± 0.126
Group P Mean ± S.D	0.791 ± 0.142	0.789 ± 0.127	0.792 ± 0.134	0.789 ± 0.127
ANOVA	0.85	0.71	0.112	0.08
P	0.389	0.61	0.921	0.958
Creatinine Clearness				
Group C Mean ± S.D	107.64 ± 11.412	107.44 ± 11.273	107.52 ± 11.046	107.48 ± 10.993
Group D Mean ± S.D	109.72 ± 12.164	110.16 ± 11.799	109.32 ± 12.061	109.28 ± 11.628
Group P Mean ± S.D	107.76 ± 13.590	108.12 ± 13.189	108.04 ± 13.151	108.1 ± 12.86
ANOVA	1.12	1.41	0.87	1.09
P	0.365	0.210	0.65	0.38

Table 2. Comparison between the cystatine C and NGAL in the three studied groups at different period of follow up. (Mean ± S.D).

	Baseline (Preoperative)	After Induction	12 h post-operative	24 h post-operative
Cystatine C				
Group C Mean ± S.D	0.974 ± 0.159	0.963 ± 0.155	0.987 ± 0.154	0.991 ± 0.158
Group D Mean ± S.D	1.035 ± 0.155	0.950 ± 0.104	0.633 ± 0.059	0.630 ± 0.048
Group P Mean ± S.D	1.057 ± 0.126	1.104 ± 0.129	1.151 ± 0.116	1.197 ± 0.099
ANOVA	1.61	1.8	6.98	7.28
P	0.09	0.042*	0.011*	0.002*
NGAL				
Group C Mean ± S.D	71.68 ± 9.437	89.04 ± 10.454	130.64 ± 10.214	153.48 ± 8.186
Group D Mean ± S.D	67.72 ± 9.813	65.08 ± 13.708	62.88 ± 16.774	58.32 ± 17.413
Group P Mean ± S.D	68.92 ± 8.775	118.2 ± 20.232	154.32 ± 13.079	178.16 ± 7.232
ANOVA	4.25	12.85	16.58	25.8
P	0.041*	0.002*	0.001*	0.001*

*significantly different between the three studied groups ($p < 0.05$)

Regarding Urine output, it seems to be significantly higher in Dex. group at all times of measurements ($p < 0.05$) except baseline values (post induction) where values did not vary significantly in either of the studied groups (Figure 2).

The amounts of intraoperative fentanyl consumed, as well as the total amount of postoperative i.v paracetamol consumption were significantly less in the Dex. Group ($p = 0.003$, $p = 0.001$, respectively) relative

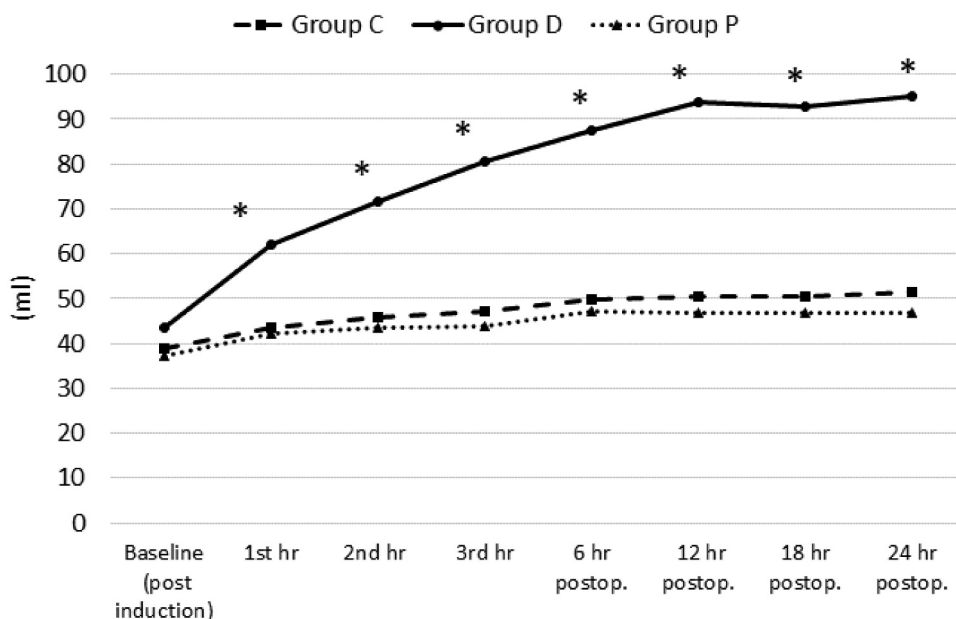


Figure 2. Comparison between the mean urine output in the three studied groups at different period of follow up.

Table 3. Comparison between the three studied groups according to objective pain score at different period of follow up.

	Group D	Group C	Group P	ANOVA	P
(T ₁) arrival to ICU (Mean ± SD)	2.6 ± 0.707	2.92 ± 0.759	5.32 ± 0.9	18.96	0.001*
(T ₂) 2 h postoperative (Mean ± SD)	2.28 ± 0.458	2.4 ± 0.866	4.4 ± 1.041	13.51	0.005*
(T ₃) 4 h postoperative (Mean ± SD)	2.2 ± 0.408	2.4 ± 0.764	4.04 ± 0.841	12.7	0.006*
(T ₄) 8 h postoperative (Mean ± SD)	2.28 ± 0.678	2.36 ± 0.81	4.32 ± 0.988	10.8	0.008*
(T ₅) 12 h postoperative (Mean ± SD)	2.28 ± 0.678	2.48 ± 0.77	4.32 ± 0.9	10.1	0.0091*
(T ₆) 16 hrs postoperative (Mean ± SD)	2.2 ± 0.645	2.12 ± 0.726	4.08 ± 0.862	11.5	0.007*
(T ₇) 24 h postoperative (Mean ± SD)	2.2 ± 0.577	2.12 ± 0.726	3.72 ± 0.792	4.21	0.015*

* Significant difference between the three groups ($p < 0.05$)

Table 4. Comparison between the sedation score in the three studied groups at different period of follow up.

	Group D	Group C	Group P	ANOVA	P
5 Mins	1.92 ± 0.16	0.6 ± 0.054	0.44 ± 0.04	18.65	0.001*
15 mins	1.28 ± 0.107	0.44 ± 0.04	0.32 ± 0.027	17.85	0.0013*
30 mins	1.04 ± 0.08	0.28 ± 0.025	0.16 ± 0.015	20.11	0.001*
60 mins	0.92 ± 0.077	0.12 ± 0.011	0.08 ± 0.007	11.2	0.005*

*significantly different between the three studied groups ($p < 0.05$)

to the other two groups. There was no need to give postoperative fentanyl as a second rescue analgesic in any of the three groups.

Also, patients in the Dex. group showed significantly lower objective pain score values ($p < 0.05$) (Table 3) and were significantly more sedated than the other two groups at all times of measurement ($p < 0.05$) (Table 4).

6. Discussion

Convenient choice of anaesthesia technique can modify various patient outcomes. Although there is no standard protocol is proved premium than other, preservation of kidney function after radical nephrectomy in children is one of the primary objectives in this type of surgery.

In the current study, there was no statistically significant difference between the three studied groups as regards to serum creatinine and creatinine clearance at all times of measurements. Also, Dex. infusion led to increase in urine output.

In agreement with our study, Zhai et al. [24] investigated the effects of Dex. on renal function in 72 patients scheduled for cardiac valve replacement under cardiopulmonary bypass. Patients were randomly allocated into Dex. group where 0.6 µg/kg/hr was given 15 min before induction, followed by 0.2 µg/kg/hr until the end of operation and Placebo group where patients were treated with normal saline equally. Results of conventional renal function tests were not significantly different. The intraoperative urine output was significantly increased in Dex. group.

In line with our results was the study carried by Leino et al. [25] on 87 patients who underwent Coronary artery bypass grafting with extracorporeal circulation. Dex. was infused after induction and continued for 4 h postoperatively. Dex. infusion was associated with an increase in urine output, although did not alter renal function, as compared with placebo.

In contrast to our results, Xie et al. [26] evaluated the effect Dex. on AKI in 82 children undergoing congenital heart surgery with cardiopulmonary bypass. The children in the Dex. group were injected with Dex. (1 µg/kg) followed by infusion with Dex. (0.5 µg/kg/h) until 12 h after operation. The Dex. group had significantly lower levels of serum creatinine values comparing to the placebo group.

The underlying mechanism by which Dex. exerts its reno-protective effect is multifactorial [27,28]. Several advances revealed stimulation of alpha-2 agonists, inhibits surgical neuro-hormonal stress response with subsequent decrease of catecholamine release, thus providing hemodynamic stability and optimum renal condition. Also, nitric oxide mediated vasodilation process occurs due to selective α₂ adrenoceptor, which are numerous in the renal peritubular structure with resultant increase in renal blood flow and glomerular filtration rate. Moreover, diuresis occurs via inhibition of renin and arginine- vasopressin system leading to decrease of sodium and water reabsorption. Additionally, current evidence demonstrated the role of Dex. in kidney protection from reactive oxygen peroxides generated during ischemia - reperfusion phases in radical nephrectomy [27–29].

Regarding serum cystatin C, the present study demonstrated that it decreased significantly in the DEX. group relative to the other two groups at all times of measurement with no significant difference between the caudal and the placebo groups except preoperative baseline values of the three groups which did not vary significantly.

In support of our results, Bai et al. [30] in a study on 177 patients with renal calculi who underwent percutaneous nephrolithotomy. Dex. was infused in 91 patients during surgery and 86 patients were used as

control group. The research group showed a significantly lower level of BUN, and cystatin C compared with the control group.

In contrast to our results, Novaes et al. [31] in their study on patients undergoing prostatectomy or nephrectomy. Dex. group received 0.5 µg /kg/h followed by 0.7 µg /kg/h and placebo group received normal saline instead. There was no significant change as regards Serum creatinine and serum cystatin C for both groups.

In the present study, there was a statistically significantly decrease in serum NGAL values in the Dex. group compared with the other two groups at all times of measurements except preoperative baseline values of the 3 studied groups which did not vary significantly ($p = 0.09$).

Suriyachote et al. [32] noted in their study on the renoprotective effect of intraoperative Dex. Infusion in elective coronary artery bypass graft, that participants in the Dex. group had significantly lower levels of serum NGAL.

In contrast to our study, one study performed by Bayram et al. [33] concluded that intraoperative Dex. infusion was not found in favor of renal function in terms of serum NGAL when evaluating the effects of Dex infusion on early renal functions in patients undergoing percutaneous nephrolithotomy.

The correlation between evaluation of the kidney function using ordinary markers (serum creatinine and creatinine clearance), with the new predictors (serum cystatin C and NGAL) revealed a negative significant correlation in the Dex. group ($r = -0.078$, $P = 0.001$) relative to non-Dex. groups which revealed no correlation. This reflects delayed response of the Conventional renal markers to early phase of renal tubular stress, and goes in favor of the peculiar markers cystatin C and NGAL as a superior diagnostic tool in predicting early kidney injury.

Caudal anaesthesia, although providing adequate hemodynamic stability, but the resultant sympathectomy and the increase in renal blood flow did not offer renal protection perse as it was expected. This is obvious from the results of the present study. In line with our results, Suleiman et al. [34] in a study on a 13 healthy volunteers concluded that the sympathetic blockade resultant from epidural anaesthesia did not alter significantly renal blood flow.

In contrast to our study, the meta analysis performed by Rodgers et al. [35] on 141 trials concluded that the incidences of acute kidney deterioration is diminished for neuraxial anaesthesia relative to general anaesthesia. However, the discrepancy between studies could be attributed to different doses, agents used and various surgical techniques.

The sedation scores in the present study were significantly higher in the Dex. group compared to the other two groups. This was not surprising due to the fact of sedative properties of Dex.

In agreement with our results, Manasa et al. [36] in their study concluded that single Dex. dose infused over 20 min could provide adequate sedation and analgesia with no concomitant respiratory depression.

The present study revealed that the non-Dex groups had significantly higher objective pain score values and consumed larger amount of analgesia (weather intraoperative fentanyl or postoperative i.v paracetamol) relative to the Dex. group at all times of measurements. Also the total number of patients who needed postoperative rescue analgesia in the non-Dex. groups was significantly higher than those in the Dex. group. This is not surprising as several evidences had reported that the analgesic potency of Dex. is mediated via stimulation of α -2C and α -2A adrenoceptors located in abundant in an area in the brain called locus ceruleus and in the dorsal horn of the spinal cord, thus decreasing release of neurotransmitters substance p and glutamate with the resultant hyperpolarization of spinal neurons and inhibition of pain propagation [27,28].

In line with our results, Priye et al. [37] investigated Dex. as an adjunct to the analgesia protocol in cardiac surgery using a dose of 0.4 µg/kg/h which continued for 12 h postoperatively. Normal saline was infused in the control group instead. Whenever VAS score exceeded 5, 25 µg i.v. fentanyl was used. Dex. group had significantly lower VAS values, additionally lower fentanyl consumption.

A potential weakness of the study is the most common adverse effects associated with Dexmedetomidine (hypotension and bradycardia), but these hemodynamic changes were not clinically significant and did not require any intervention.

7. Conclusion

The present study established that the technique using dexmedetomidine is proved to be superior in preservation of kidney functions after radical nephrectomy in children and detection of early kidney injury using cystatin C and NGAL biomarkers.

Disclosure statement

No potential conflict of interest is declared.

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