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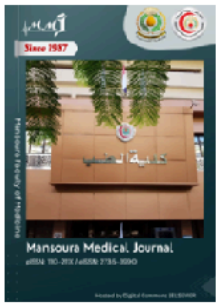

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Opioid-Free Anaesthesia During Prolonged Orthotopic Urinary Bladder Diversion Surgery: A Prospective Randomized Comparative Study

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ORIGINAL STUDY

Opioid-free Anesthesia During Prolonged Orthotopic Urinary Bladder Diversion Surgery: A Prospective Randomized Comparative Study

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Abstract

Background: **Opioid-free anesthesia is becoming a favored strategy among anesthetists. This study aims to compare continuous epidural fentanyl infusion with an intrathecal bolus of bupivacaine-dexmedetomidine, which is a low-cost analgesic technique with efficient intraoperative hemodynamic stability, postoperative analgesia, and fewer opioid-induced drawbacks in urinary bladder diversion surgery.**

Patients and methods: **Our randomized prospective comparative study involved 34 patients prepared for urinary bladder diversion surgery. Patients were distributed into two equivalent groups; group A received continuous epidural infusion of bupivacaine-fentanyl, and group B received intrathecal bolus bupivacaine-dexmedetomidine.**

Results: **Intraoperatively, the heart rate showed a significant decrease at 2 h in group B (71.82 ± 8.76 vs. 79.41 ± 12.56) ($P = 0.049$) in compared to group A. Mean blood pressure displayed a significant decrease in group B than in group A at 1, 1.5, 2, 2.5, and 3 h ($P < 0.001$). The total consumption of intravenous fentanyl in the first 24-h postoperative was significantly decreased in group B compared to group A ($P = 0.014$).**

Conclusion: **Opioid-free anesthesia using intrathecal dexmedetomidine is an efficient, harmless strategy that allows better control of sensory and motor block levels, provides hemodynamic stability, and avoids cumulative opioid-induced complications. It can be used as an alternate option to continuous epidural anesthesia in patients undergoing prolonged urinary bladder diversion surgery.**

Keywords: Cancer bladder, Continuous epidural, Dexmedetomidine, Opioid-free anesthesia, Urinary diversion

1. Introduction

Opioid-free anesthesia has becomes a favored strategy among anesthetists. The strategy includes using anesthesia without intraoperative opioids neither systemic, neuraxial, nor intracavitary (Sultana et al., 2017).

Epidural analgesia is the keystone of pain alleviation in thoracic and abdominal surgeries. Additionally, it has been a keystone of any enhanced recovery after surgery pathway planning for colorectal surgery (Borzellino et al., 2016).

Lipophilic opioids such as fentanyl stay longer in the epidural space by segregation into epidural fat; moreover, during continuous epidural infusion of lipophilic opioids, the analgesic effect and the plasma concentration of such drugs are the same as that of intravenous infusion (Tomulić Brusich et al., 2023). Combining epidural opioids and local anesthetics provides higher analgesia (additive or synergistic) in comparison with utilizing one of them alone while reducing the dose-related adverse effects (Mazy et al., 2019). Graduated dosing of epidural opioids and local anesthetic concentrations should be carried out to gain an equity between offering the best analgesia and evading hemodynamic instability (Guasch et al., 2020).

Dexmedetomidine usage as an additive to bupivacaine in subarachnoid anesthesia was reported to prolong motor block, sensory block, and analgesia

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postoperatively (Rahimzadeh et al., 2018; Paramasivan et al., 2020). Additionally, it reduces 24-h pain severity and reduces the occurrence of shivering with no increase in other unfavorable drawbacks (Shen et al., 2020).

This study aims to compare continuous epidural fentanyl infusion with intrathecal bolus of bupivacaine-dexmedetomidine. The primary outcome was the entire dose of i.v. fentanyl consumed throughout the earliest 24 h postoperatively. The secondary outcomes were intraoperative heart rate (HR) and mean arterial blood pressure (MAP) and postoperative HR, MAP, visual analog scale (VAS) score and side effects such as bradycardia, hypotension, desaturation, and vomiting incidence.

2. Patients and methods

Our randomized, nonblinded prospective comparative research was enrolled in a clinical trial registry with code number NCT05262166. After approval of the Institutional Review Board of our medical school (MS.21.10.1699), this research was done at Mansoura Urology and Nephrology Centre, Mansoura University and was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013). Written consent was obtained from every patient before surgery.

Thirty-four patients of both sexes, aged 21–70 years with American Society of Anesthesiologists physical status II, anticipated for urinary bladder diversion prolonged surgery, are included in this study. The exclusion criteria were patient rejection, allergy to the research drugs, decompensated liver, kidney, or lung disease, and any contraindication to subarachnoid or epidural anesthesia.

The computer-generated program randomly distributed all participants into two equivalent groups, 17 patients in each group, according to random number codes that were located in closed envelopes.

Group A (epidural fentanyl) (n = 17): applying epidural catheter set, 5 ml of bupivacaine 0.5% and 50 μg fentanyl with added saline 0.9% making a total volume of 40 ml (0.0625% bupivacaine with 1.25 μg fentanyl/ml). Bolus epidural injection of 15 ml, then epidural infusion at a rate of 3–5 ml/h of the same drug concentration and dilution along operation.

Group B (intrathecal dexmedetomidine) (n = 17): at L3–4 spinal level, intrathecal bolus injection of 3 ml bupivacaine 0.5% (15 mg) with 10 μg dexmedetomidine.

2.1. Sample size calculation

Sample size calculation was done by the PASS program, with a power of 90% and an alpha error of 5%. The outcomes of earlier research (Alansary and Elbeialy, 2019) revealed that the mean opioid consumption was 18.9 ± 3.4 μg in the dexmedetomidine group, compared with 23.3 ± 3.2 μg in the fentanyl group. Using two sample *t* tests allowing unequal variance, the required sample size was 26 patients. A 20% dropout is considered, so 34 patients were enrolled.

2.2. Preoperative preparation

In the ward, standard evaluation was performed on all patients by meticulous history taking, precise clinical assessment, and laboratory investigations. The procedure was explained to each participant, and written consent was obtained from him/her the day before surgery. In addition, they have learned the way to exhibit their pain by the VAS: scored from 0 to 10 (where 0 = no pain and 10 = the worst pain ever).

In the preanesthesia room, basic monitoring, including a pulse oximeter, noninvasive blood pressure, and ECG, was performed, and baseline data were documented. After that, insertion of 20-G intravenous cannula and preloading by 500 ml sodium chloride (NaCl 0.9%) solution over 30 min before anesthesia.

2.3. Intraoperative management

Basic monitoring by pulse oximetry, noninvasive blood pressure, and ECG while the patient was in a sitting position with neck and upper back flexed. In group A (epidural fentanyl group): under an aseptic technique, 2 ml of lidocaine 2% was infiltrated in the skin nearly 1 cm lateral to the lower aspect of the aimed spinous process (L3–4). Local infiltration of subcutaneous tissues was done to attain sufficient anesthesia along the planned pathway. An epidural Tuohy needle (18 G) was introduced in place and advanced through the skin, subcutaneous tissue, supraspinous, and interspinous ligaments. Stylet was dislodged, and the luer lock (loss of resistance) syringe that was filled with saline was attached to the needle. Once loss of resistance was achieved, stabilization of the needle, threading the catheter into epidural space in the cephalic direction, and securing the catheter was done. Epidural injection of bolus of 15 ml of previously prepared injectate, then epidural infusion in a rate of 3–5 ml/h was done. In group B (intrathecal dexmedetomidine group), under aseptic technique, local infiltration with 2 ml of lidocaine 2% was done, and dural puncture was performed using a 25-G Quincke needle at 3–4 l interspaces. After observing the free flow of the cerebrospinal fluid, 3 ml (15 mg) of

hyperbaric bupivacaine 0.5% and 10 μg dexmedetomidine was injected. Patients in both groups lay down in a supine position. Sensory and motor blocks were assessed. After T6 sensory block to pin-prick and Bromage grade 3 motor block were achieved, general anesthesia was induced by pre-oxygenation for 5 min, injection of propofol 2 mg/kg slowly and atracurium 0.5 mg/kg, then proper placement of endotracheal tube and initiation of mechanical ventilation with tidal volume 7 ml/kg, respiratory rate 12, positive end expiratory pressure 7 and both tidal volume and respiratory rate adjusted to keep end tidal CO_2 in the range 30–35 mmHg, then anesthesia was maintained by isoflurane inhalation of 1 MAC and atracurium dosing of 0.1 mg/kg when needed.

Intraoperatively, HR, and MAP were monitored and recorded every 30 min. Any incidence of hypotension (MAP<60 mmHg or fall >20% below baseline value) was managed by using i.v. 6 mg ephedrine. Colloid, blood, and/or plasma transfusion were given as just the patients' needs. Bradycardia (HR < 60 beats/min) was managed by i.v. 0.5 mg atropine. After completion of the surgery, residual neuromuscular block was reversed using i.v. (neostigmine 0.04 mg/kg and atropine 0.02 mg/kg), and after fulfilling the criteria of extubation, patients were extubated, moved to the recovery room, and discharged to the ward the next day.

2.4. Postoperative management

Postoperatively, all patients received i.v. paracetamol 10 mg/kg every 8 h, patients with VAS more than 3 received i.v. fentanyl 50 μg. The entire dose of fentanyl consumed throughout the earliest 24 h postoperatively was recorded.

2.5. Data collected

The primary outcome was the entire dose of i.v. fentanyl consumed throughout the earliest 24 h postoperatively in both groups. The secondary outcomes were intraoperative HR and MAP every 30 min all over the operation time and at 1, 6, 12, and 24 h after recovery. The patient's VAS pain score was evaluated at 1, 2, 6, 12, 18, and 24 h after recovery (Khosravi et al., 2020). Postoperative side effects as bradycardia, hypotension, desaturation, and vomiting incidence during recovery and through the first 24 h.

2.6. Statistical analysis and data interpretation

Data analysis was performed by SPSS software, version 18 (SPSS Inc., PASW statistics for Windows version 18; SPSS Inc., Chicago, Illinois, USA). Qualitative data were described using numbers and percents. Quantitative data were described using median (minimum and maximum) for nonnormally distributed data and mean ± SD for normally distributed data after testing normality using Shapiro–Wilk test. The significance of the obtained results was judged at the (0.05) level. χ^2, Fisher exact, and Monte Carlo tests were used to compare qualitative data between groups as appropriate. Mann–Whitney *U* test was used to compare the two studied groups for nonnormally distributed data. Student *t* test was used to compare two independent groups for normally distributed data.

3. Results

In our study, 34 participants were involved (17 participants in each group) (Fig. 1).

There was no statistically significant variance in demographic data among the two groups (Table 1). The total consumption of intravenous fentanyl analgesia in the first 24-h postoperative significantly declined in group B in comparison to group A ($P = 0.014$) (Table 2). HR showed a significant decrease at 2 h during intraoperative period in group B (71.82 ± 8.76 vs. 79.41 ± 12.56) ($P = 0.049$) in compared to group A, while no significant difference was registered afterward (Table 3). MAP displayed a significant decline in group B than in group A intraoperatively at 1 h (73.59 ± 6.94 vs. 93.82 ± 15.86), at 1.5 h (75.47 ± 7.16 vs. 87.88 ± 10.71), at 2 h (76.24 ± 10.18 vs. 90.82 ± 9.57), at 2.5 h (78.18 ± 9.13 vs. 93.18 ± 8.43), and at 3 h (84.12 ± 10.28 vs. 93.0 ± 9.25) all with ($P < 0.001$) while no significant difference was registered afterward (Table 4). Group B has statistically significant lower pain VAS scores at 12 and 18 h when compared to group A (Fig. 2). There were not any registered cases of intraoperative bradycardia, postoperative bradycardia, or oxygen desaturation in either group (Table 5).

4. Discussion

So far as we know, this randomized controlled research is the earliest to evaluate the efficacy of intrathecal bolus of bupivacaine-dexmedetomidine analgesia compared to traditional continuous epidural fentanyl infusion analgesia. We hypothesized that intrathecal bolus of bupivacaine-dexmedetomidine analgesia (a low-cost analgesic strategy) can replace traditional epidural fentanyl infusion analgesia (the keystone of pain relief in abdominal surgeries) with efficient intraoperative hemodynamic

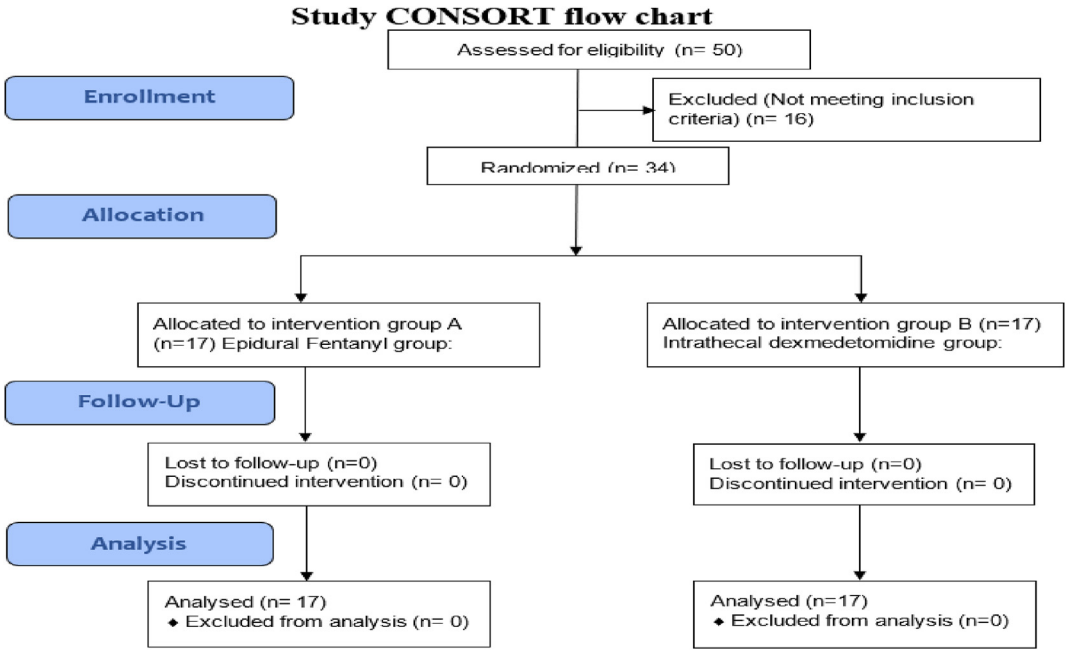

Fig. 1. Flowchart demonstrating recruitment of patients in both study groups.

Table 1. Demographic characteristics of the studied groups.

	Group A	Group B	*P* value
Age/years (mean ± SD)	61.06 ± 6.94	60.82 ± 9.32	0.939
BMI (kg/m^2) (mean ± SD)	26.19 ± 3.98	28.0 ± 3.67	0.177
Sex [*n* (%)]			0.545
Male	1 (5.9)	2 (11.8)	
Female	16 (94.1)	15 (88.2)	

Group A, epidural fentanyl group; Group B, intrathecal dexmedetomidine group.

Table 2. Postoperative total fentanyl consumption in the study groups.

	Group A	Group B	*P* value
Total dose of fentanyl/μg	*N* = 16	*N* = 17	0.014*
Median (min.–max.)	150 (100–250)	100 (50–200)	

Group A, epidural fentanyl group; Group B, intrathecal dexmedetomidine group; min, minimum; max, maximum.

stability and postoperative analgesia, and fewer opioid-induced drawbacks in urinary bladder diversion surgery.

In the current research, we compared the intraoperative hemodynamic changes. The overall fentanyl needs postoperatively, patient's VAS, and incidence of complications (intraoperative and postoperative) between the two studied groups in

Table 3. Heart rate changes (beat/min) between study groups.

HR (beat/min) (mean ± SD)	Group A	Group B	*P* value
Basal	88.35 ± 15.17	81 ± 13.76	0.149
After block	87.29 ± 14.14	80.65 ± 12.98	0.163
After induction	88.24 ± 13.55	79.94 ± 12.87	0.08
0.5 h	83.94 ± 12.93	75.12 ± 14.29	0.068
1 h	74.94 ± 12.77	74.76 ± 13.36	0.969
1.5 h	79.06 ± 11.54	72.82 ± 10.13	0.104
2 h	79.41 ± 12.56	71.82 ± 8.76	0.049*
2.5 h	77.88 ± 12.97	73.52 ± 10.75	0.295
3 h	81.35 ± 15.17	78.53 ± 12.28	0.555
3.5 h	80.35 ± 13.22	82.06 ± 12.16	0.698
4 h	81.06 ± 16.44	82.18 ± 10.80	0.816
4.5 h	81.29 ± 16.67	83.65 ± 10.54	0.626
5 h	86.0 ± 17.29	85.76 ± 10.35	0.962
5.5 h	87.29 ± 15.12	87.12 ± 10.78	0.969
6 h	87.59 ± 14.32	88.88 ± 13.35	0.787
6.5 h	89.24 ± 13.91	90.12 ± 12.04	0.844
7 h	88.12 ± 12.05	89.12 ± 13.62	0.822
7.5 h	90.88 ± 10.80	88.18 ± 10.38	0.470
8 h	90.73 ± 10.94	89 ± 10.51	0.651
8.5 h	93.27 ± 12.13	94.92 ± 12.68	0.721
9 h	90.70 ± 8.59	95.60 ± 9.26	0.236
9.5 h	93.50 ± 11.27	95.29 ± 6.65	0.730
10 h	108.50 ± 9.19	98.0 ± 10.81	0.346
After recovery	108.50 ± 9.19	98.29 ± 10.82	0.438
1 h after recovery	86.24 ± 11.23	90.41 ± 12.87	0.321
6 h after recovery	90.76 ± 10.03	89.76 ± 11.13	0.785
12 h after recovery	88.65 ± 11.61	87.94 ± 10.7	0.855
24 h after recovery	87.94 ± 11.29	87.53 ± 10.25	0.912

Group A, epidural fentanyl group; group B, intrathecal dexmedetomidine group; HR, heart rate.

Table 4. Mean arterial blood pressure changes between study groups.

MAP (mmHg) (mean ± SD)	Group A	Group B	*P* value
Basal	98.84 ± 13.23	98.82 ± 9.37	0.976
After block	87.47 ± 15.21	86.35 ± 11.63	0.811
After induction	82.12 ± 14.53	73.76 ± 10.93	0.067
0.5 h	80.41 ± 10.55	82.59 ± 9.55	0.533
1 h	93.82 ± 15.86	73.59 ± 6.94	<0.001*
1.5 h	87.88 ± 10.71	75.47 ± 7.16	<0.001*
2 h	90.82 ± 9.57	76.24 ± 10.18	<0.001*
2.5 h	93.18 ± 8.43	78.18 ± 9.13	<0.001*
3 h	93.0 ± 9.25	84.12 ± 10.28	0.012*
3.5 h	90.24 ± 10.97	87.35 ± 8.18	0.392
4 h	89.29 ± 8.56	89.05 ± 11.21	0.946
4.5 h	87.53 ± 7.36	84.12 ± 12.79	0.348
5 h	87.41 ± 9.33	87.24 ± 9.50	0.957
5.5 h	88.47 ± 10.09	92.94 ± 10.17	0.208
6 h	90.12 ± 10.30	87.88 ± 10.02	0.526
6.5 h	89.29 ± 8.06	91.76 ± 12.88	0.507
7 h	89.35 ± 9.11	90.65 ± 9.01	0.680
7.5 h	90.64 ± 7.48	91.31 ± 8.55	0.813
8 h	90.12 ± 9.03	92.31 ± 9.03	0.490
8.5 h	91.57 ± 13.34	94.13 ± 8.52	0.532
9 h	88.60 ± 7.59	94.0 ± 8.72	0.148
9.5 h	84.57 ± 7.11	94.50 ± 13.49	0.117
10 h	92.33 ± 9.50	80.0 ± 5.67	0.207
After recovery	91.12 ± 12.57	92.18 ± 11.39	0.799
1 h after recovery	85.24 ± 11.55	89.41 ± 9.19	0.252
6 h after recovery	86.65 ± 9.89	87.71 ± 10.09	0.759
12 h after recovery	85.41 ± 10.17	86.59 ± 10.02	0.736
24 h after recovery	86.88 ± 8.74	84.18 ± 8.62	0.370

Group A, epidural fentanyl group; Group B, intrathecal dexmedetomidine group; MAP, mean arterial blood pressure.

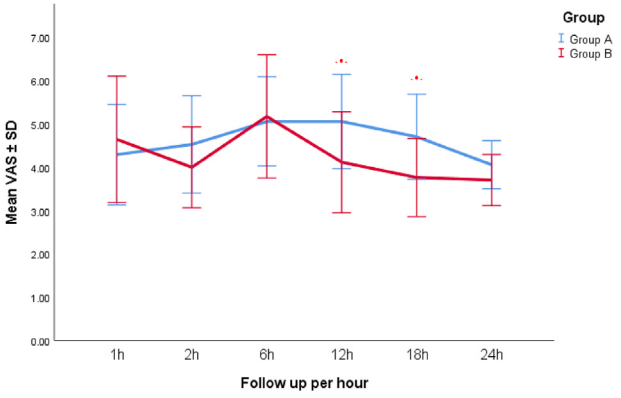

*Fig. 2. Visual analog scale (VAS) score during follow-up among the study groups. Data are expressed as mean ± SD. Group A, epidural fentanyl group; Group B, intrathecal dexmedetomidine group. *P value is considered significant when less than 0.05.*

patients undergoing prolonged urinary bladder diversion surgery.

We found that total consumption of intravenous fentanyl analgesia in the first 24-h postoperative was significantly lowered in group B in comparison to group A. HR, when compared between both groups, showed insignificant variation, but there was a significant reduction only at 2 h in group B when correlated to group A. Nevertheless, clinically, there was not any significant hemodynamic instability, and none of the patients required any active intervention. In addition, MAP revealed a significant reduction in group B when compared to group A. According to VAS, group B showed a significant decrease in VAS than group A. As regards postoperative complications, there was insignificant variation between both groups.

General anesthesia was applied because general anesthesia is the most common anesthetic modality used for prolonged urinary bladder diversion surgery. This could be owing to better agreement by patients, the facility to increase the surgery time, and/or the anesthetist may favor general anesthesia.

In our study, we combined spinal with general anesthesia to gain the benefit of both techniques as performing a lengthy operations with decreased intraoperative hemodynamic instability, postoperative pain, and opioid consumption, which matched with Segal et al. (2014), who found that pain scores and analgesic consumption during the earliest 24 h after robotic sacro-cervicopexy operation were significantly decreased with combined subarachnoid and general anesthesia compared to general anesthesia alone.

The current study showed that intraoperative HR when compared between both groups, showed insignificant variation, but there was a significant reduction only at 2 h in group B in comparison to group A. However, clinically, there was not any significant hemodynamic instability, and none of the patients required any active intervention.

MAP also showed a significant reduction intraoperatively in group B, nearly at 1, 1.5, 2, 2.5, and 3 h, when compared to group A.

Our results are supported by the study of Alansary and Elbeialy, who randomized adult patients planned for elective lumbar discectomy or laminectomy into two equal groups: group 1 (bupivacaine-dexmedetomidine) and group 2 (bupivacaine-fentanyl). They concluded that the incidence of intraoperative hypotension and bradycardia increased significantly in the bupivacaine-dexmedetomidine group than in the bupivacaine-fentanyl group (Alansary and Elbeialy, 2019).

This could be explained by a combination of spinal and general anesthesia. Also, this may be due to the stimulation of presynaptic α-2 receptors by dexmedetomidine, so that reducing norepinephrine release, leading to a drop in HR and blood pressure. The bradycardic impact of dexmedetomidine is

Table 5. Intraoperative and postoperative complications in the study groups.

Complications as number (percentage)	Group A	Group B	*P* value
Incidence of intraoperative hypotension			
Negative	15 (88.2)	14 (82.4)	1.0
Positive	2 (11.8)	3 (17.6)	
Incidence of intraoperative bradycardia	0	0	
Incidence of postoperative hypotension			1.0
Negative	16 (94.1)	17 (100)	
Positive	1 (5.9)	0	
Incidence of postoperative bradycardia	0	0	
Incidence of postoperative desaturation	0	0	
Incidence of postoperative vomiting	2 (11.8)	1 (5.9)	1.0

Group A, epidural fentanyl group; Group B, intrathecal dexmedetomidine group.

mainly due to a reduction in sympathetic tone and partially owing to baroreceptor reflex and augmented vagal activity (Lee, 2019).

Postoperative VAS score in this research revealed insignificant variation between both groups at 1, 2, and 6 h. While group B showed a significant decrease when compared to group A at 12 h. In addition, the total consumption of intravenous fentanyl analgesia in the first postoperative 24 h was significantly reduced in group B in comparison to group A. These findings were in correlation with Alansary and Elbeialy and Saiyad and colleagues, who documented that using dexmedetomidine is an excellent alternative to fentanyl as a beneficial adjuvant to intrathecal bupivacaine, which provides a better quality of intraoperative analgesia, least drawbacks and decreased need for analgesics in the first postoperative 24 h in comparison with fentanyl (Alansary and Elbeialy, 2019; Saiyad et al., 2021).

Our results showed insignificant variation in the occurrence of detrimental effects, apart from a decreased incidence of postoperative vomiting in the intrathecal dexmedetomidine group than the epidural fentanyl group. This is matched with Kalbande colleagues, who found that nearly 6–10% of the participants had pruritus, nausea, and vomiting in the fentanyl group in comparison to no one in the dexmedetomidine group, which may prolong postoperative improvement and discharge. Nevertheless, intraoperative complications were statistically indifferent between the two groups (Kalbande et al., 2022). It is also in association with the study of Frauenknecht and colleagues which was a meta-analysis of 23 randomized controlled studies including 1304 patients. They concluded that opioid-based anesthesia did not decrease postoperative pain scores or opioid need; however, it is accompanied by a greater incidence of postoperative nausea and vomiting, which may prolong postoperative improvement and discharge (Frauenknecht et al., 2019).

4.1. Conclusion

Opioid-free anesthesia using intrathecal dexmedetomidine is an efficient, harmless strategy that provides valuable postoperative analgesia, affords hemodynamic stability, and avoids cumulative opioid-induced complications. Moreover, it is a low-cost, streamlined, easy, and simple technique. Therefore, it can be used as an alternate option to continuous epidural anesthesia in patients undergoing prolonged orthotopic urinary bladder diversion surgery.

Ethics information

The study adhered to the Declaration of Helsinki, and approved by the Institutional Review Board of our medical school (Mansoura faculty of medicine) (MS.21.10.1699).

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Disclosure statement

The authors report no financial or non-financial conflicts of interest in this work.

Conflict of interest

There are no conflicts of interest.

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