Original Article

Intraoperative administration of systemic/epidural/intrathecal morphine on the quality of recovery following substitutional urethroplasty with buccal mucosal graft: A randomized control trial

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Abstract

Background and Aims: Substitutional urethroplasty with buccal mucosal grafting for urethral stricture is associated with significant pain, and thus inappropriate perioperative pain management could delay postoperative recovery. The objective of our research was to determine the effects of analgesia with systemic or epidural or intrathecal morphine on quality of recovery (QoR) in patients undergoing substitutional urethroplasty with buccal mucosal grafting.

Material and Methods: This prospective, double-blinded, randomized control trial was conducted over 2 years in ASA I and II patients who underwent substitutional urethroplasty with buccal mucosal graft. Patients were randomized into three groups, and Group A received systemic morphine (0.1 mg/kg), Group B received epidural morphine (3 mg), and Group C received intrathecal morphine (150 μg). The QoR between the groups were compared postoperatively using the 40-item QoR questionnaire, and the hemodynamic variations, time taken for ambulation, resumption of oral intake, and incidence of complications were also compared.

Results: Out of the recruited 93 patients, 88 patients were analyzed. The QoR score for each domain was comparable between the three groups. The total QoR score for systemic, epidural, and intrathecal morphine groups were 189 (185–191), 189 (187–191), and 185 (183–189), respectively. Additionally, the hemodynamic variations, time taken for ambulation, and resumption of oral intake were comparable between all three groups except the incidence of postoperative nausea and vomiting (PONV) and pruritis, which were higher in the intrathecal group.

Conclusion: All three modalities, namely systemic morphine (0.1 mg/kg), epidural morphine (3 mg), and intrathecal morphine (150 μg), offer similar QoR after substitutional urethroplasty. However, the incidence of PONV and pruritis was higher with the administration of intrathecal morphine.

Keywords: Morphine, pain management, postoperative pain, spinal injection, urethral stricture

Introduction

Urethral stricture is a common urologic disease, which affects 300 per 100,000 males and often presents with symptoms of urinary tract obstruction, infection, and sexual dysfunction, which significantly affects the quality of life.[1] Moreover, the treatment of urethral stricture is a complex and challenging task due to the high rates of recurrence.[2]

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Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.JOACP_589_20

How to cite this article: Johnson JP, Arumugam R, Karuppusami R, Mariappan R. Intraoperative administration of systemic/epidural/intrathecal morphine on the quality of recovery following substitutional urethroplasty with buccal mucosal graft: A randomized control trial. J Anaesthesiol Clin Pharmacol 2022;38:537-43.

Submitted: 06-Oct-2020 **Revised:** 14-Apr-2021
Accepted: 17-Apr-2021 **Published:** 29-Nov-2022

The perineal area has an immense nerve supply, which is associated with significant perioperative pain. So, inadequate postoperative analgesia could cause unpleasant effects like chronic pain.[3,4] On the contrary, overzealous pain management could result in undesirable effects like postoperative nausea and vomiting (PONV), over sedation, respiratory depression, pruritis, and delayed recovery.[5,6] Therefore, optimal pain control is essential to facilitate early postoperative recovery.[7,8] Although postoperative pain is an essential component of quality of recovery (QoR), assessment of pain alone does not entirely address the full dimensions of postoperative recovery.

With the recent advancements in anesthetic and surgical techniques, the focus of healthcare is being shifted toward improving the QoR.[8] To date, no studies looked at the adequacy of postoperative analgesia and their effect on QoR following substitutional urethroplasty with a buccal mucosal graft.A 40-item QoR questionnaire (QoR-40) is a validated tool to assess the effect of interventional procedures on QoR,[9,10] which measures five dimensions of recovery, namely pain, nausea and vomiting, physical independence, physical comfort, emotional state, and psychological support.

In our institution, 100–150 substitutional urethroplasties with buccal mucosal graft are performed each year, for which three modes of analgesic techniques are practiced, namely administration of systemic opioids (fentanyl, morphine), epidural fentanyl with bupivacaine, and intrathecal morphine with bupivacaine. Hence, we wanted to study the QoR in patients undergoing urethroplasty needing buccal graft using QoR-40 questionnaire.

The primary objective of our research was to compare the effects of intraoperative administration of systemic, epidural, and intrathecal morphine on the QoR at 24 h after substitutional urethroplasty with a buccal mucosal graft using the QoR-40 questionnaire. The secondary objectives were to compare the intraoperative and postoperative analgesic requirement, hemodynamic status, the incidence of postoperative complications such as PONV, pruritis, and respiratory depression during the first 24 h after surgery. The time of ambulation and the length of hospital stay were compared between the three groups.

Material and Methods

The principal aim of our research was to determine the superior mode of a perioperative analgesic technique on QoR among systemic, epidural, and intrathecal morphine. With the approval of the Institutional Review Board (IRB Number 10285) and ethics committee, we conducted a prospective, double-blinded, randomized control trial between November 2016 and November 2018. Informed consent was taken from the all the study participants before enrolling them into the study. We have included ASA I and II patients aged between 18 and 60 years with a normal renal function who underwent substitutional urethroplasty with buccal mucosal graft, while patients with ASA status III and IV, BMI >30, obstructive sleep apnea, impaired renal function (serum creatinine >1.4 mg/dl), and moderate to severe chronic obstructive lung disease and those who had contraindications for regional anesthesia were excluded.

On the day before surgery, informed consent was obtained, and a detailed explanation was provided to the patients regarding the QoR questionnaire and use of patient-controlled analgesia (PCA) pump by the principal investigator (PI). Patients were informed that the epidural/intrathecal injection would be given either before or after the start of general anesthesia according to the discretion of the attending anesthesiologist to ensure the patient blinding.

On the day of surgery, after establishing the standard ASA monitors, a wide bore peripheral line was inserted under local anesthesia, and 500 ml of 0.9% saline preloading was done. The randomization envelope was opened in the operating room by the attending anesthesiologist, and the standard study protocol was followed according to the group to which the patient got allocated.

Apart from conventional anesthetic drugs used for induction and intubation, all our patients received appropriate analgesics as per the randomization. Thus, Group A received 0.1 mg/kg of intravenous (i.v) morphine as an intermittent bolus over 30 min after induction, prior to the surgical incision. While patients in Group B received 3 mg of epidural morphine suspended in 5 ml of 0.2% bupivacaine at the L3–L4 or L4–L5 epidural space prior to induction. Likewise, Group C received 150 μg intrathecal morphine in 1 ml of 0.5% heavy bupivacaine at L4–L5 or L5–S1 subarachnoid space prior to induction. We followed the block randomization process to ensure equal allocation and appropriate allocation concealment was maintained by means of a sealed envelope method. The randomization schedule was generated using SAS software version 9.4. The treating physician left the operating room after the time-out procedure until the patient was ready to be positioned, thereby the treating surgeons were also blinded.

All patients were anesthetized using a standard anesthetic protocol. Induction was carried out using fentanyl (2 mcg/kg) and propofol (2 mg/kg) and paralysis with

vecuronium (0.1 mg/kg). After 3 min of ventilation, patients were intubated with a nasal endotracheal tube (ETT) with an additional dose of fentanyl (0.5 μg/kg) and propofol (0.5 mg/kg) to attenuate the hemodynamic response, and appropriate depth of anesthesia was maintained with 0.8–1 minimum alveolar concentration (MAC) of isoflurane in air and oxygen. After securing the nasal ETT, a throat pack was applied to prevent aspiration of blood during the buccal graft harvest. Additionally, i.v paracetamol (20 mg/kg) and dexamethasone (0.1 mg/kg) were administered before the surgical incision for analgesia and prevention of PONV, respectively. Thereafter, the intraoperative pain response was treated with 0.5 μg/kg of fentanyl. The buccal mucosa was harvested after infiltrating the mucosa with 8–10 ml of 2% xylocaine with 1 in 2 lakh epinephrine.

Intraoperatively, the hemodynamics was maintained within 20% of their baseline reading. At the end of the surgery, the patients were extubated and shifted to the recovery room, where they were closely monitored for 1–2 h. In the meantime, a morphine-filled continuous ambulatory drug delivery (CADD) pump was connected to a separate i.v line, and the patients were encouraged to use the pump when their pain score was >3. Patients weighing <70 kg received 1 mg of morphine per bolus on demand, whereas those weighing >70 kg, had received 1.2 mg/bolus with the lockout period of 10 min. Also, 20 mg/kg of i.v paracetamol and ondansetron 0.1 mg/kg was given postoperatively at regular intervals. While shifting the patient to a ward, the anesthesia record was stapled to blind the PI about the intraoperative intervention details. The PI was involved only in following-up of patients in the ward and in collecting the QoR-40 questionnaire at 24 h. Since all patients were on i.v. morphine PCA during the postoperative period, the blinding was ensured for patients, surgeon, and the PI.

The baseline demographic details, associated comorbidities, and the intraoperative parameters, such as hemodynamics, intraoperative opioid requirement, blood loss, and the amount of intravenous fluid administered were studied. Postoperatively, the hemodynamics were studied in the post anaesthesia care unit (PACU) and the ward at various time intervals for 24 h. Pain at the buccal site and the urethral site was documented separately using a numerical rating scale (NRS 0–10) at the various interval for 24 h. Incidence of complication, such as PONV, pruritis, respiratory depression, and level of sedation, was noted both in the PACU and in the ward at regular intervals during the first 24 h postoperative period. All patients were attended by the PI at the end of 24 h, and the QoR was assessed using the QoR-40 questionnaire. The total dose of morphine consumption, a total number of PCA attempts at the end of 24 h, the ambulation time, and length of hospital stay after surgery were noted and compared between the three groups.

The sample size was calculated with reference to the study by Mariappan *et al*.[11] in which they have compared the effect of an analgesic technique (systemic opioids versus regional blockade) on QoR as the primary outcome. To achieve a mean difference of 22 points in QoR between the systemic and the neuraxial groups, with a 90% power and two-sided test, the number needed was 31 patients in each group with the total number of 93 patients.

Statistical analysis

Descriptive statistics of mean ± SD was used to report data that followed a normal distribution, whereas the median (IQR 25, 75) was used to report the skewed data. The categorical data were expressed as number and percentage. Subsequently, the parametric ANOVA and nonparametric Kruskal–Wallis test were employed depending on the normality of data to test for the presence of any significant difference between the groups. The Kruskal–Wallis test was performed to detect the significant difference in each domain of the QoR score between the groups. The repeated measures ANOVA test was used to find the significant change over time between groups on the pain score at the urethral site and the buccal site at a various time intervals. To identify changes in the vital parameters over time between groups, the generalized estimating equations analysis was utilized. All tests were two sided at $\alpha = 0.05$ level of significance and analyzed using the Statistical Package for Social Services software version 21.0 (Armonk, NY, USA: IBM Corp).

Results

A total of 105 patients were screened; of which, 12 patients were excluded as they failed to meet the inclusion criteria, and thus 93 patients were recruited. The consort flow diagram is presented in Figure 1. Out of the recruited 93 patients, two patients in Group A and Group B and one in Group C did not undergo the planned procedure. A total of 88 patient results were analyzed. There were no statistically significant differences in the patient demographics and the intraoperative variables [Table 1] between the groups except for the anesthesia duration, which was prolonged in the epidural group compared to other two groups.

The aggregated global QoR-40 score (median [IQR: 25th, 75th percentile]) at the 24 h postoperative period was similar between all three groups. The total QoR score with median (IQR) for the systemic, epidural, and intrathecal morphine groups were 189 (185, 191), 189 (187,191), and 185 (183,189), respectively [Table 2]. The total, as well

as the individual score for each domain of QoR, have failed to achieve any statistical significance among the groups and thereby indicate that no technique is superior to the other in terms of improving the QoR.

Pain at the perineal site and the buccal site were compared (NRS 0–10) between the three groups at a various time interval during the first 24 h. The mean pain score between the groups both at the perineal and the buccal site is depicted in Figure 2a and b. It was comparable between the groups without statistical significance.

The total opioid consumption and the total attempts of PCA made during the first 24 h were comparable between the groups with the *P* value of 0.79 and 0.95, respectively [Table 1]. Similarly, the hemodynamics were compared stable in the first 24 h as seen by the trends of heart rate and the mean blood pressure in Figure 3a and b. Moreover, none of the participants was deeply sedated or had respiratory depression.

In terms of resuming oral intake and ambulation time, there was no difference between the groups, and all patients were started on oral fluids after 4 h of reaching ward and were ambulated on the first postoperative day. Those who had vomiting were kept nil per oral for 2 h, and again the oral fluids were restarted. The mean duration of hospital stay was 4 days following the surgery without any significant difference between the three groups.

However, the incidence of PONV and pruritis was higher in intrathecal morphine group compared to the other two groups, as illustrated in Table 3. The incidence of postoperative nausea achieved a statistical significance at arrival in PACU in the intrathecal group.

Discussion

In our trial, we demonstrated that all three analgesic techniques, namely systemic, epidural, and intrathecal morphine, were

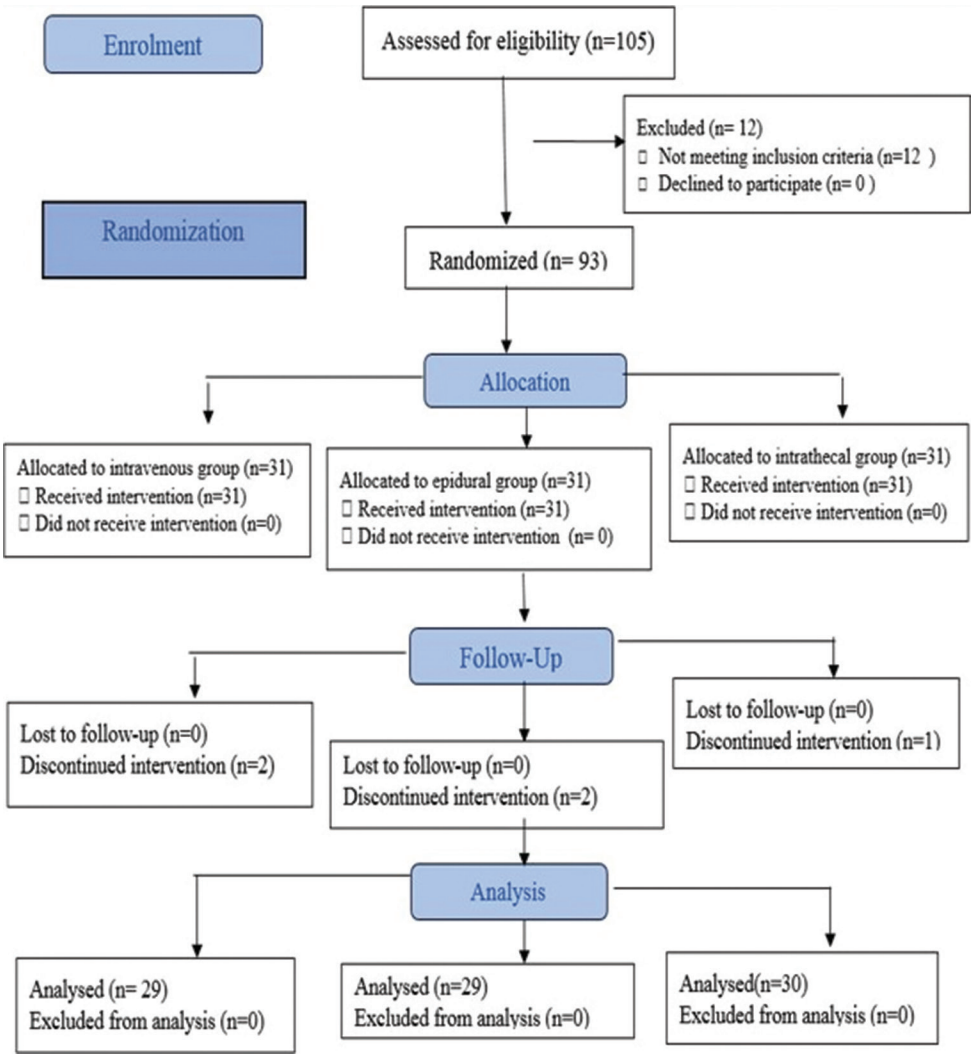

Figure 1: Consort flow diagram

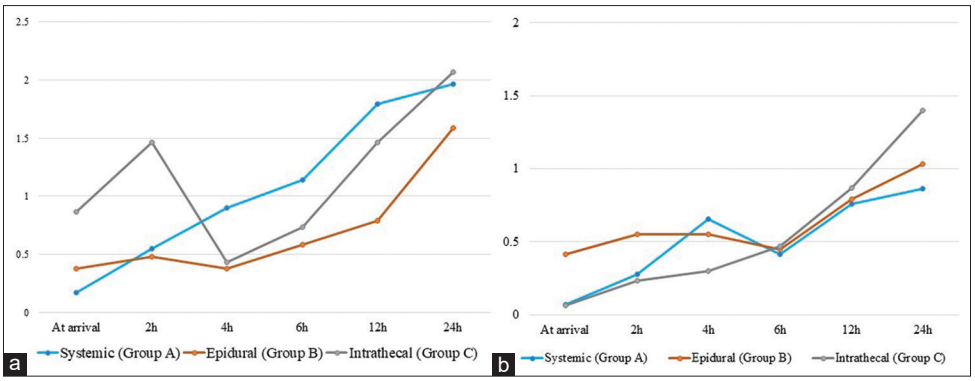

Figure 2: The mean NRS score at the (a) perineal and (b) buccal site during the first 24 h postoperative period

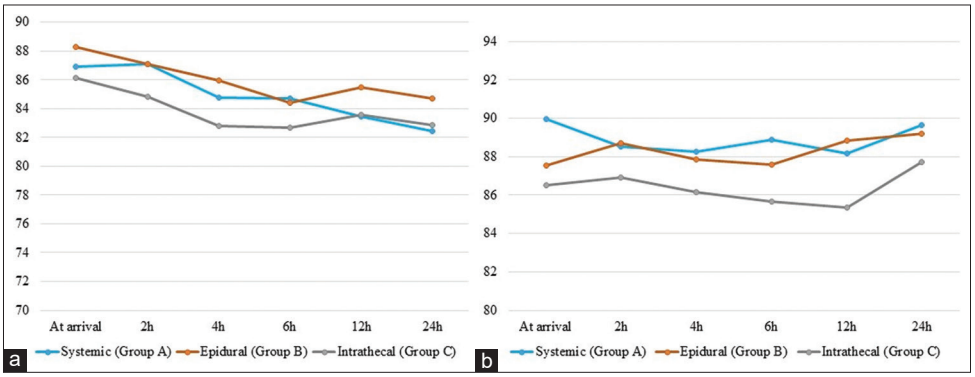

Figure 3: (a) The heart rate and (b) the mean blood pressure at various time intervals during the first 24 h postoperative period

Table 1: Demographic, intraoperative, and postoperative details of patients in all the three groups

Parameters	Group A (*n*=29) Systemic Morphine (Mean±SD)	Group B (*n*=29) Epidural Morphine (Mean±SD)	Group C (*n*=30) Intrathecal Morphine (Mean±SD)	*P*
Age (years)	38.2±11.9	40.7±12.9	39.5±12.1	0.74
Weight (kg)	70.4±10.2	68.5±13.8	88.4±11.5	0.61
Height (cm)	168.3±6.5	165.9±7.1	161.1±20.1	0.14
BMI	24.8±3.3	24.7±3.8	25.6±4.3	0.60
Comorbidities†				
Diabetes Mellitus	4	6	1	0.13
Hypertension	7	5	1	0.07
Asthma	1	1	0	0.59
Intraoperative and Postoperative Parameters				
Total dose of Propofol (mg/kg)	2.7±0.8	2.7±0.6	2.4±0.6	0.11
Total dose of fentanyl (μg/kg)	3.1±0.7	3.2±0.6	3.0±0.9	0.42
Blood loss (ml)	720.7±1228.0	584.5±504.5	513.3±199.5	0.58
Crystalloids (ml)	1877.6±624.7	2182.8±882.8	1748.3±696.1	0.08
Colloids (ml)	241.4±287.3	396.6±363.0	250±286.1	0.11
Duration of surgery (min)	233.1±67.5	262.0±77.0	232.2±67.6	0.20
Duration of anesthesia (min)	264.5±72.2	305.5±75.6	262.2±69.4	0.04
Total attempts made in CADD pump (*n*)‡	7 (2, 10)	7 (3, 15)	7 (3, 15)	0.95
A total dose of morphine received first 24 h postop (mg)‡	4 (1.5, 8.5)	4 (2, 9)	6 (1.75, 10.25)	0.79

†*Represented as a number;* ‡*Median (interquartile range 25,75)*

comparable in terms of the QoR in patients undergoing substitutional urethroplasty with buccal mucosal grafting. For instance, the total QoR scores ranged high enough (185–189 points) for all three groups indicating that both systemic and neuraxial opioids provided equivalent analgesia and reduced the postoperative morphine consumption and its related side effects during the first 24 h thereby improved the QoR. Overall, those who received intrathecal morphine

Table 2: Comparison of the total score and score for each domain in quality of recovery between groups

Quality of Recovery Parameters	Group A Systemic morphine (Median [IQR])	Group B Epidural Morphine (Median [IQR])	Group C Intrathecal Morphine (Median [IQR])	*P*
Patient comfort	58 (58, 60)	59 (57, 60)	58 (57, 60)	0.24
Emotional state	45 (44, 45)	44 (44, 45)	44 (42.8, 45)	0.37
Physical independence	17 (15, 18)	18 (16, 19)	17 (15, 18)	0.14
Patient support	35 (35, 35)	35 (35, 35)	35 (35, 35)	0.46
Pain	33 (32, 34)	34 (33, 34)	33 (33, 34)	0.32
Total quality of recovery score	189 (185, 191)	189 (187, 191)	185 (183, 189)	0.08

Table 3: The incidence of complications between all three groups

Parameters	Group A Systemic Morphine	Group B Epidural Morphine	Group C Intrathecal Morphine	*P*
In PACU				
Nausea	2 (6.8%)	1 (3.4%)	8 (26%)	0.01
Vomiting	1 (3.4%)	1 (3.4%)	3 (10%)	0.45
Pruritis	0	0	3 (10%)	0.06
In the ward				
Nausea	6 (20%)	2 (6.8%)	9 (30%)	0.08
Vomiting	4 (13%)	1 (3.4%)	7 (23%)	0.08
Pruritis	1 (3.4%)	2 (6.8%)	5 (16%)	0.19
Headache	4 (13%)	1 (3.4%)	2 (6.8)	0.33
Backache	3 (10%)	1 (3.4%)	3 (3.4%)	0.55

scored slightly lesser than the systemic and epidural group (185 versus 189), which could be explained by the higher incidence of PONV and pruritis in this group.

The optimal neuraxial opioid dose is defined as the dose that provides adequate analgesia with minimal side effects.[12] We chose to administer 0.1 mg/kg of morphine intravenously as it is the routine standard practice for analgesia for this procedure in our institution. Likewise, we administered 150 μg and 3 mg of morphine via intrathecal and epidural route, respectively, as these doses are considered as the optimal neuraxial opioid dose based on the studies available in the literature.[13-15] Compared to the standard intravenous administration, the doses that we used provided equivalent analgesia without any significant complications like respiratory depression or excessive sedation or excessive PONV and the pruritis.

More frequently, patients experience pain from both buccal graft site and perineal site after substitutional urethroplasty with buccal mucosal graft, as these areas receive very dense nerve supply. Very often, the pain from the mucosal graft site is overlooked. However, we have assessed the pain score separately for both the sites and observed that out of 88 patients, 58 patients (65%) did not complain of pain at the buccal graft site; this may be due to the pre-emptive analgesic effect of local anesthetic infiltration. Among the 30 patients who had pain at the buccal site, 15 (17%) had only mild pain, and the rest 15 (17%) patients had moderate pain with the pain score of 4–5. Dublin *et al*.[16] looked at the complication after the buccal mucosal graft harvesting and found that 75% of the population had no to mild pain, which is similar to our study findings.

Yorukoglu *et al*.[17] compared the postoperative analgesia and the hemodynamics of intrathecal morphine (100 μg), epidural (2 mg) morphine, and local infiltration and shown that both neuraxial techniques provided adequate analgesia and hemodynamic stability. However, we have used a slightly higher dose compared to this study and demonstrated satisfactory analgesia without any hemodynamic instability.

On the other hand, Lim *et al*.[18] had studied the effects of three modes of morphine on postoperative pain and its related side effects following caesarean section and concluded that neuraxial opioid was associated with lower pain scores at rest and movement compared with intravenous morphine. In contrary, in our trial, the pain domain of QoR-40 score for systemic, epidural, and intrathecal morphine group was 33, 34, and 33, respectively ($P = 0.32$), which indicates that all three approaches provided equivalent and effective analgesia for this surgery and the mean pain scores were comparable between the groups.

Although other studies[17-19] have shown a reduction in the postoperative opioid consumption with neuraxial opioids, there was no significant difference in overall morphine consumption with neuraxial opioids in our study. However, we noticed that the systemic morphine group had less postoperative

morphine consumption, which could be due to the pre-emptive administration of multimodal analgesic drugs before the surgical incision. Similarly, the study by Kilickan *et al*.[20] had shown that pre-emptive administration of 0.15 mg/kg intravenous morphine reduced the postoperative opioid consumption.

In our study, mean total QoR score was high; this could be explained by the pre-emptive administration of analgesic drugs before the surgical stimulus, the satisfaction of controlling the pain by the patients themselves using IV PCA, and the frequent visit and the positive motivation of the study investigators and the acute pain team members. Studies have shown that the removal of anxiety and fear can reduce postoperative opioid consumption, which signifies the psychological impact on acute pain management.[21] The pain component of QoR is similar between the three groups; this could be explained by the psychological impact on acute pain management.

The CADD pumps do not have the feature to record the first dose of administration of the drug and the amount of opioid consumed at 6 and 12 h. So, we could not analyze the exact consumption of morphine at 6, 12, and 24 h separately. Such information could have provided a better insight regarding the postoperative morphine requirement with each technique at various time points. Also, QoR should have also been assessed at 48 h after surgery as well.

Conclusion

In terms of available analgesic options for substitutional urethroplasty with buccal mucosal grafting, all three techniques, intraoperative administration of systemic morphine (0.1 mg/kg), epidural morphine (3 mg), and intrathecal morphine (150 μg), offer similar QoR. The incidence of PONV and pruritis is higher with the administration of intrathecal morphine.

Financial support and sponsorship
Internal Fluid research grant was obtained to conduct the study (IRB minute number 10285).

Conflicts of interest
There are no conflicts of interest.

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