Hospitalization for partial nephrectomy was not associated with intrathecal opioid analgesia: Retrospective analysis

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ABSTRACT

Background: The aim of this retrospective study is to test the hypothesis that the use of spinal analgesia shortens the length of hospital stay after partial nephrectomy. **Materials and Methods:** We reviewed all patients undergoing partial nephrectomy for malignancy through flank incision between January 1, 2008, and June 30, 2011. We excluded patients who underwent tumor thrombectomy, used sustained-release opioids, or had general anesthesia supplemented by epidural analgesia. Patients were grouped into "spinal" (intrathecal opioid injection for postoperative analgesia) versus "general anesthetic" group, and "early" discharge group (within 3 postoperative days) versus "late" group. Association between demographics, patient physical status, anesthetic techniques, and surgical complexity and hospital stay were analyzed using multivariable logistic regression analysis. **Results:** Of 380 patients, 158 (41.6%) were discharged "early" and 151 (39.7%) were "spinal" cases. Both spinal and early discharge groups had better postoperative pain control and used less postoperative systemic opioids. Spinal analgesia was associated with early hospital discharge, odds ratio 1.52, (95% confidence interval 1.00-2.30), $P = 0.05$, but in adjusted analysis was no longer associated with early discharge, 1.16 (0.73-1.86), $P = 0.52$. Early discharge was associated with calendar year, with more recent years being associated with early discharge. **Conclusion:** Spinal analgesia combined with general anesthesia was associated with improved postoperative pain control during the 1st postoperative day, but not with shorter hospital stay following partial nephrectomy. Therefore, unaccounted practice changes that occurred during more recent times affected hospital stay.

Key words: *Hospital length of stay, neuroaxial anesthesia, radical nephrectomy*

INTRODUCTION

Enhanced recovery surgical pathways have been adopted in colorectal surgery to reduce the length of hospitalization.[1] These protocols emphasize mitigation of physiologic stress and expedited return to normal function. Less attention has been paid to enhanced recovery surgical pathways for partial nephrectomy surgery. Only two studies have evaluated recovery pathways for open transperitoneal and partial nephrectomies, and demonstrated that the length of hospital stay can be shortened.[2,3] Urologists at our institution have continually focused on improving outcomes of their surgical patients. Practice improvement initiatives starting in 2001 have included several pathways for partial nephrectomy, which have been continually modified. Some of the examples of practice changes include early resumption of diet, early ambulation, and attention to improvements in postoperative pain control. The current departmental goal is to achieve discharge on the 3rd postoperative day.

One tenant of enhanced recovery is optimal pain control with emphasis placed on neuroaxial analgesia.[1] However, the efficacy of neuroaxial analgesia to achieve earlier discharge has been controversial. A Cochrane review found that perioperative epidural anesthesia provides better pain control, but not earlier discharge.[4] Of the two nephrectomy studies examining enhanced protocols, one did not use neuroaxial analgesia,[2] while the other

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employed epidural analgesia for all patients,[3] which prevents examining the role of neuroaxial analgesia on outcome. Several years ago our practice increased use of intrathecal opioid analgesia for patients undergoing partial nephrectomy with the postulate that this modality would improve pain control while decreasing systemic opioids, and this combination, in turn, would reduce hospital stay. However, implementation of this practice has not been uniform.

Our primary aim was to examine whether the spinal analgesia is associated with goal hospital discharge within 3 days following partial nephrectomy. In addition, because reducing the immediate postanesthesia recovery room (postanesthesia care unit [PACU]) stay may result in more efficient flow of surgical patients in centers with large patient volumes, a secondary endpoint was set that is, to determine whether the use of intrathecal analgesia shortens the Phase I postoperative recovery.

MATERIALS AND METHODS

This study was approved by the Mayo Clinic, Rochester MN, Institutional Review Board consistent with Minnesota Statute 144.335 Subd. 3a. (d), we included only patients who have provided authorization for research use of their medical records (historically >95% of Mayo Clinic patients).[5]

Study design

We designed a retrospective study to assess whether intrathecal opioid analgesia was associated with an increase percentage of patients who were discharged in ≤3 days. This observational cohort study is in accordance with the STROBE statement [www.strobe-statement.org].

Study setting

This study was set at a large academic tertiary care facility.

Population studied

The Mayo Clinic Department of Urology nephrectomy registry was used to identify all adult patients who had partial nephrectomy for renal malignancy between January 1, 2008, and June 30, 2011. In order to study a homogeneous patient population, we included in our review only patients undergoing partial nephrectomy through flank incision. We excluded nephrectomies associated with tumor thrombectomy, any reoperations, as well as patients who were preoperatively using sustained-release opioids.

Anesthetic management

Patients were managed with either a general anesthetic (GA group) or a GA supplemented with a single intrathecal injection (spinal group) of a hydrophilic opioid (i.e., preservative free morphine or hydromorphone) that was administered prior to induction of general anesthesia. The choice of anesthetic management was made by the attending surgeon and anesthesiologist based on clinical judgment.

After completion of surgery patients were transferred to the PACU for Phase I recovery. During Phase I recovery, registered nurses continuously monitored patients for four respiratory specific events: Hypoventilation (three episodes of <8 respirations/min); apnea (episode of apnea ≥10 s); hypoxia (three episodes of oxyhemoglobin saturations as measured by pulse oximetry [pulse oxygen saturation <90% with or without nasal cannula]); and "pain/sedation mismatch" (defined as Richmond Agitation Sedation Score[6] = −3 - −5 and a numeric pain score >5 [from a scale 0 (no pain) to 10 (worst pain imaginable)]).[7,8] Any patient who has a respiratory specific event must have a subsequent 60 min period free of further events in order to be transferred to a nonmonitored ward. Otherwise discharge criteria for Phase I recovery are based on modified Aldrete criteria.[9] Postoperative pain management for patients consisted of administration of systemic opioids initially through a patient controlled analgesia device and then through oral medications.

Data abstraction

Data were abstracted from electronic medical records and entered manually into the web-based Research Electronic Data Capture (REDCap®) system (version 3.6.7, Vanderbilt University, Nashville, Tennessee).[10] Records were abstracted for demographics, preoperative, intraoperative and postoperative variables including age, sex, body mass index (BMI), preoperative hemoglobin concentrations, and the presence of multiple renal tumors. Overall physical status was assessed from the American Society of Anesthesiologists physical status (ASA PS) score. Abstracted data included anesthetic duration and management (GA vs. spinal), blood transfusions, the course of Phase I recovery including duration, administration of systemic opioids, episodes of severe pain (numeric pain score ≥7),[11] the occurrence of any respiratory specific events, unplanned use of continuous positive airway pressure (CPAP), or naloxone administration. The doses of systemic opioid analgesics were converted to intravenous morphine equivalents using published guidelines.[12]

The postoperative course was reviewed for hospital length of stay, Intensive Care Unit (ICU) admissions, and unplanned use of CPAP, naloxone administration, occurrence of severe pain, and systemic opioids during the first and second 24 postsurgical periods. Postoperative complications were considered if they were of Grade IV severity (life-threatening complication requiring intensive

care management, e.g., low output heart failure) using the Dindo *et al.*[13] surgical complications classification system.

Data analysis

The primary outcome variable of interest was hospital discharge within 3 postoperative days. Therefore, our cohort of patients was dichotomized into early and late discharge categories (≤3 days vs. >3 days). The primary explanatory variable was intrathecal analgesia. The potential association between patient characteristics and early hospital discharge was assessed using univariate and multivariable logistic regression analyses of preoperative characteristics as explanatory variables. In addition, a stratified logistic regression analysis was performed using five strata defined based on the propensity for receiving intrathecal analgesia. For this analysis, propensity scores were obtained for each individual using a multiple logistic regression model with spinal analgesia as the dependent variable. Explanatory variables for this model included age, sex, BMI, ASA PS, presence of multiple tumors, preoperative hemoglobin concentration and calendar year of surgery. Study patients were then divided into five strata based on quintiles of the propensity scores with Cochran-Mantel-Haenszel statistics and linear models used to verify that baseline characteristics were similar between anesthesia groups after adjusting for propensity strata.

Data are presented for continuous variables using mean ± standard deviation, or median (25^{th}, 75^{th} percentile), and for categorical variables by number and (percentages). Findings from the logistic regression analyses are summarized with odds ratio (OR) and 95% confidence intervals [CI]. Two-tailed $P \leq 0.05$ were considered as statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

During the study time-frame 380 patients met the inclusion criteria. The anesthetic technique was GA without spinal analgesia in 229 (60.3%) and GA with spinal analgesia in 151 (39.7%). The proportion of surgeries performed using spinal opioid analgesia increased over calendar time (24.6% [2008-2009] vs. 62.5% [2010-2011], $P < 0.01$). There was variation in the medications used for intrathecal injections: All patients received hydrophilic opioids with 88 (58.3%) hydromorphone, 61 (40.4%) morphine, and 2 patients not specified; 78 (51.7%) received bupivacaine; and 20 (13.2%) received clonidine. Preoperative patient characteristics are summarized in Table 1.

Of the patients who received spinal analgesia, 72 (47.7%) were discharged within 3 days, and of the patients received GA only 86 (37.6%) were discharged within 3 days (unadjusted OR: 1.52 95% CI: 1.00-2.30, $P = 0.05$). After adjusting for other explanatory variables the use of spinal analgesia was no longer found to be significantly associated with earlier hospital discharge (propensity stratified OR: 1.16 95% CI: 0.73-1.86, $P = 0.52$) [Table 2].

Table 3 shows variables related to the surgical and postoperative course according to anesthetic type. The spinal group had longer anesthetic duration reflecting additional time needed to perform the intrathecal injection. Patients who had spinal analgesia had shorter Phase I recovery time and better pain control with less opioid use in the PACU and over the first 24 postoperative hours.

In order to gain insight into characteristics associated with discharge within 3 days a *post-hoc* analysis was performed to compare variables related to surgical and postoperative course between those discharged within days versus those with longer hospital stays [Table 4]. The intraoperative course for patients discharged within 3 days was characterized by a shorter duration of anesthesia, less opioids, and fewer blood transfusions. These patients had shorter Phase I recovery time and better pain control with less opioid use throughout the first 48 postoperative hours. Patients admitted to the ICU were less likely to be discharged within 3 days.

DISCUSSION

Our main finding was that the patients undergoing partial nephrectomy, who received intrathecal opioid analgesia, were not more likely to be discharged within 3 days compared with those who received general anesthesia only. While intrathecal opioid was found to provide better postoperative pain management, the effect was limited to the first 24 h. However, adequate pain management appears to be an important element of earlier discharge, as patients

Table 1: Characteristics of patients undergoing partial nephrectomy through flank incision by anesthetic type*

Variable	Spinal *n* = 151	General *n* = 229	*P*
Age, years	57.9±12.1	60.7±11.9	0.03
Male sex	88 (58.3)	153 (66.8)	0.09
BMI (kg/m²)	31.0±6.3	30.4±6.6	0.45
ASA PS	2 (2,3)	2 (2,3)	0.88
Hemoglobin (g/dL)	14.0±1.4	14.0±1.5	0.76
Multiple tumors	11 (7.3)	18 (7.9)	1.00

Values are displayed as mean ± SD, number (%) or median (25%, 75% quartile ranges); Percentages represent proportion of either spinal or general groups; *Anesthetic type was spinal analgesia combined with general anesthetic (spinal) versus general anesthetic only; BMI: Body mass index; ASA PS: American Society of Anesthesiologists physical status; SD: Standard deviation

Table 2: Patient characteristics associated with early hospital discharge

Variable	LOS <3 days (*n* = 158)	LOS >3 days (*n* = 222)	Univariable analysis§			Multivariable analysis§		
			OR	95% CI	*P*	OR	95% CI	*P*
Spinal analgesic								
No	86 (37.6)	143 (62.4)	1.00	Reference	0.05	1.00	Reference	0.52
Yes	72 (47.7)	79 (52.3)	1.52	1.00-2.30		1.16	0.73-1.86	
Age at surgery (years)	57.8±11.7	60.9±12.1	0.98	0.96-1.00	0.01	0.98	0.96-1.00	0.03
Gender								
Male	99 (41.1)	142 (58.9)	1.00	Reference	0.79	1.00	Reference	0.77
Female	59 (42.4)	80 (57.6)	1.06	0.69-1.62		1.07	0.66-1.74	
Body mass index (kg/m²)*	30.5±6.0	30.7±6.7	1.00	0.96-1.03	0.76	0.99	0.96-1.03	0.69
ASA PS								
2	98 (44.7)	121 (55.3)	1.00	Reference	0.14	1.00	Reference	0.62
3-4	60 (37.3)	101 (62.7)	0.73	0.48-1.11		0.89	0.56-1.41	
Hemoglobin (g/dL)*	14.0±1.5	14.0±1.5	1.02	0.89-1.17	0.79	1.02	0.87-1.20	0.78
Multiple tumors	12 (42.9)	16 (57.1)	1.06	0.49-2.30	0.87	1.08	0.48-2.42	0.85
Year of surgery								
2008	34 (30.9)	76 (69.1)	1.00	Reference	0.01	1.00	Reference	0.04
2009	47 (39.5)	72 (60.5)	1.46	0.84-2.52		1.50	0.86-2.63	
2010	52 (52.0)	48 (48.0)	2.42	1.38-4.25		2.39	1.31-4.37	
2011†	25 (49.0)	26 (51.0)	2.15	1.09-4.25		1.99	0.97-4.09	

Values are displayed as mean ± SD, number (%); Percentages represent proportion of each variable; *1 missing value for body mass index, 5 missing values for preoperative hemoglobin; †Dates range from January 1 to June 30 2011; §Analyses predicting hospital LOS ≤3 days, ORs above 1;0 indicate an increased probability of hospital LOS ≤3 days; LOS: Length of hospital stay; ASA PS: American Society of Anesthesiologists physical status; OR: Odds ratio, CI: Confidence interval; SD: Standard deviation

who were discharged within 3 days had significantly better analgesic management than those who stayed longer than 3 days. The percentage of patients meeting early discharge criteria increased over the calendar period of our study suggesting that in addition to pain control it is likely that other changes in practice occurred during this time, which contributed to the shortening of hospitalization.

The optimal analgesic strategy, specifically the value of neuraxial analgesia, for patients having flank incisions has not been evaluated. Two previous studies examining enhanced pathways for nephrectomy included analgesic protocols that precluded an analysis of potential benefits of neuroaxial analgesia.[2,3] Our findings suggest intrathecal analgesia provides better pain control over parentally administered opioids; however, this effect is limited to 24 postoperative hours. This study is consistent with our previous prospective trials that assessed the role of intrathecal opioids on different surgical populations.[14,15] In these prospective randomized trials of vaginal hysterectomy and radical retropubic prostatectomy surgeries, intrathecal opioids improved analgesia and reduced systemic opioid use for the first 12 postoperative hours and postoperative day, respectively.[14,15] Therefore, the present study confirms our previous findings[14,15] that intrathecal opioids provide superior analgesia that is limited to the expected duration of opioid effects.

These results are similar to a Cochrane review which found that epidural anesthesia provides superior analgesia over systemic opioids after laparotomy.[4] However, this review failed to demonstrate that epidural analgesia reduced hospitalization stay.[4] These results are similar to those of the current study and to our previous study of vaginal hysterectomy where spinal analgesia did not reduce hospital stay.[15] In our prospective randomized trial of radical prostatectomy surgery intrathecal opioids did decrease the duration of hospitalization from 2.8 to 2.1 days.[14] However, this difference was a result of five control patients with longer hospitalizations. Two of these patients had anastomotic urine leaks (surgical complication) and three delayed return of bowel function (potentially related to systemic opioids). If hospital discharge (Chi-square test) is recalculated (by us) after excluding the 2 patients with surgical complications, the duration of hospitalization becomes nonsignificant between the two study groups ($P = 0.12$).

Efficient flow of patients through surgical areas is of paramount importance in high volume medical centers. Patients with prolonged Phase I recovery times can overwhelm PACU capacity and lead to choke points in patient flow. Our spinal group had shorter Phase I recovery, suggesting this anesthetic technique may reduce utilization of PACU resources. However, these patients required more anesthetic time for placement of the block. Thus, the overall impact of this anesthetic technique on surgical flow is unclear. Other unaccounted factors may also reduce Phase 1 recovery, as patients with early discharge also had shorter Phase 1 recovery. Interestingly, neither group (spinal and

Table 3: The clinical course of patients undergoing partial nephrectomy through flank incision for renal malignancy by anesthesia type

Variable	Anesthetic type		
	Spinal* *n* = 151	General *n* = 229	*P*
Surgical course			
Duration (min)	256±62	226±70	<0.01
Systemic opioids, ME mg	29.5 (20, 35.3)	40 (33.3, 45)	<0.01
Blood transfusions	8 (5.3)	24 (10.5)	0.09
Phase I recovery course			
Duration, minutes	116±56	129±63	0.05
Systemic opioids, ME mg	2.7 (0, 10)	8 (2.5, 13.3)	<.01
Severe pain episode†	48 (32.0)	102 (45.0)	0.01
Respiratory specific events‡	27 (18.0)	44 (19.2)	0.79
Hypoventilation	18 (12.1)	32 (14.1)	0.57
Apnea	19 (12.8)	29 (12.8)	1.00
Desaturations	14 (9.4)	19 (8.4)	0.73
Pain sedation mismatch	1 (0.7)	10 (4.4)	0.04
Unplanned use of CPAP/ BiPAP	3 (2.1)	5 (2.2)	1.00
Naloxone administration	3 (2.1)	4 (1.8)	1.00
Postoperative course			
Severe pain episode, 1st 24 h†,‡‡	51 (33.8)	109 (47.6)	0.01
Systemic opioids, ME, 1st 24 h‡‡	16 (3, 48)	49.7 (26.7, 83.4)	<0.01
Severe pain episode, 2nd 24 h†	31 (20.5)	39 (17.0)	0.42
Systemic opioids, ME, 2nd 24 h	20 (7.5, 46)	26.5 (13, 53)	0.08
Intensive Care Unit admission	10 (6.6)	21 (9.2)	0.45
Unplanned use of CPAP/BiPAP	4 (2.7)	3 (1.3)	0.44
Naloxone administration	0 (0)	3 (1.3)	0.28
Life-threatening complications	2 (1.4)§	2 (1.1)¥	0.65

Values are displayed as mean ± SD, number (%) or median (25%, 75% percentile); Percentages represent proportion of either spinal or general groups; *Anesthetic type was spinal analgesia combined with general anesthetic (spinal) versus general (general) anesthetic only; †Severe pain was defined as numeric pain score ≥7;[11] ‡Respiratory specific events are assessed by registered nurses specialized in the recovery of postanesthesia patients during Phase I recovery, respiratory specific events include: Hypoventilation (three episodes of <8 respirations/min), apnea (episode of apnea ≥10 s), oxyhemoglobin desaturations (three episodes of oxyhemoglobin saturations as measured by pulse oximetry (pulse oxygen saturation <90% with or without nasal cannula), and "pain/sedation mismatch" (defined as Richmond Agitation Sedation Score[6] =−3 - −5 and a numeric pain score >5 (from a scale 0 being no pain and 10 being worst pain imaginable);as described by Gali *et al.*;[7,8] ‡‡Time measurement begins at time of discharge from PACU; §Life-threatening complications included: Myocardial infarction (1), hemorrhagic shock from bleeding renal artery pseudoaneurysm (1); ¥Life-threatening complications included: Respiratory arrest with need for reintubation (1), postoperative retroperitoneal hemorrhage complicated by a cerebellar hemispheric ischemic stroke (1); ME: Morphine equivalents;[12] CPAP: Continuous positive airway pressure; BiPAP: Bi-level positive airway pressure; PACU: Postanesthesia recovery unit; SD: Standard deviation

Table 4: The clinical course of patients undergoing partial nephrectomy through flank incision for renal malignancy according to length of hospital stay

Variable	Hospital LOS		
	Hospital LOS ≤3 days *n*=158	Hospital LOS >3 days *n*=222	*P*
Surgical course			
Duration (min)	226±64	247±71	<0.01
Systemic opioids, ME mg	34.2 (25, 42.3)	37 (29.9, 45)	0.01
Blood transfusions	3 (1.9)	29 (13.1)	<0.01
Phase I recovery course			
Duration (min)	114±55	131±64	0.01
Systemic opioids, ME mg	6.3 (0, 12)	6.7 (0, 12.8)	0.55
Severe pain episode†	50 (31.7)	100 (45.3)	0.01
Respiratory specific events‡	23 (14.6)	48 (21.7)	0.08
Hypoventilation	16 (10.1)	34 (15.6)	0.17
Apnea	13 (8.2)	35 (16.1)	0.03
Desaturations	11 (7.0)	22 (10.1)	0.36
Pain sedation mismatch	2 (1.2)	9 (4.2)	0.13
Unplanned use of CPAP/ BiPAP	2 (1.3)	6 (2.8)	0.48
Naloxone administration	1 (0.7)	6 (2.8)	0.25
Postoperative course			
Severe pain episode, 1st 24 h†,‡‡	49 (31.0)	111 (50.2)	<0.01
Systemic opioids, ME, 1st 24 h‡‡	25.2 (6.3, 65.1)	43.8 (22.9, 82.9)	<0.01
Severe pain episode, 2nd 24 h†	18 (11.4)	52 (23.7)	<0.01
Systemic opioids, ME, 2nd 24 h	14 (2.4, 32.4)	34.7 (17.3, 65.9)	<0.01
Intensive Care Unit admission	2 (1.3)	29 (13.1)	<0.01
Unplanned use of CPAP/ BiPAP	0 (0)	7 (3.2)	0.02
Naloxone administration	1 (0.7)	2 (0.9)	1.00
Life-threatening complications	0 (0)	4 (2.1)£	0.15

Values are displayed as mean±SD, number (%) or median (25%, 75% percentile); Percentages represent proportion of patients who were either discharge within or >3 postoperative days; †Severe pain was defined as numeric pain score ≥7;[11] ‡Respiratory specific events are assessed by registered nurses specialized in the recovery of postanesthesia patients during Phase I recovery as described by Gali *et al.*[7,8] and detailed in legend of Table 3; ‡‡Time measurement begins at time of discharge from PACU; £Life-threatening complications included: Myocardial infarction (1), hemorrhagic shock from bleeding renal artery pseudoaneurysm (1), respiratory arrest with need for reintubation (1), postoperative retroperitoneal hemorrhage complicated by a cerebellar hemispheric ischemic stroke (1); ME: Morphine equivalents;[12] CPAP: Continuous positive airway pressure; BiPAP: Bi-level positive airway pressure; PACU: Postanesthesia recovery unit; SD: Standard deviation

early discharge) had a reduction in overall respiratory specific events in the PACU despite less systemic opioids used during surgery and better pain control in the PACU. Therefore, respiratory adverse events during Phase I recovery may not be associated with prolonged hospital stay.

Limitations of the study

This study has inherent limitations of retrospective analyses. Since later epochs of the study [Table 2] were associated with higher likelihood for achieving early hospital discharge, this probably reflects practice changes that occurred over time. These changes embraced various components of enhanced recovery protocols with emphasis on early return to function. Since perioperative changes have been adopted gradually over time this limits our ability to retrospectively determine which factor had the most impact on the reduction of hospitalization. A further limitation is that within our practice operative variables were not standardized and the use of spinal anesthesia was heterogeneous between the anesthesiologists and surgeons.

CONCLUSION

The use of intrathecal analgesia for partial nephrectomy was associated with improved immediate postoperative pain management, a pattern consistent with the expected effects of intrathecally administered opioids. The use of intrathecal opioids *per se* was not associated with shorter hospitalization.

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