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Benefits of a Multimodal Regimen for Postsurgical Pain Management in Colorectal Surgery

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Background: Postoperative pain management is a major concern and a significant component of postoperative care pathways for surgery patients.

Methods: We performed a retrospective medical record review of 233 consecutive patients undergoing major colorectal surgery from October 2011 to January 2013 at an academic medical center. All patients were managed with similar enhanced recovery pathways; 66 patients received multimodal postsurgical pain management that included liposomal bupivacaine intraoperatively, and 167 patients received conventional pain management with intravenous opioids. Comparisons were made using *t* test and chi-square analysis with StatView (SAS Institute Inc.).

Results: Patients receiving multimodal pain management with liposomal bupivacaine injected in the surgical site at the end of major colorectal procedures had lower postoperative pain scores and used significantly less opioids at 12, 24, 36, 48, 60, and 72 hours (P=0.03). Patients in the multimodal group also had a significantly decreased risk of opioid-related adverse events, with decreased use of antipruritic medications and antiemetic medications postoperatively. A significant decrease in length of postoperative hospital stay was seen in the multimodal group (7.2 vs 9.0 days, P=0.04).

Conclusion: The use of multimodal pain management including liposomal bupivacaine during major colorectal surgeries improved postoperative outcomes, decreased lengths of stay, and increased bed availability.

Keywords: *Bupivacaine, combined modality therapy, pain management, postoperative care*

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INTRODUCTION

Postoperative pain management is a major concern and a significant component of postoperative care pathways for surgery patients. In national surveys, 80% of patients undergoing surgery report pain that is moderate, severe, or extreme in intensity during the first 2 weeks postprocedure.[1,2] A multimodal approach to postoperative pain management using a combination of different classes of analgesics provides superior pain relief and minimizes opioid use and opioid-related adverse events.[3,4]

While opioids are effective and continue to be a mainstay of postsurgical pain management, opioid-related adverse events are common, and the clinical and economic consequences associated with these events are significant.[5,6] Adverse events such as respiratory depression, drowsiness and sedation, postsurgical nausea and vomiting, pruritus, urinary retention, and ileus can lead to increased costs and prolonged lengths of stay. These adverse events seem to correlate with the amount and duration of opioid usage. Previous studies suggest that a reduction in opioid-related adverse events may result in shorter lengths of hospital stay and lower hospital costs.[4,7]

Additional multimodal pain medications have recently become available to manage postoperative pain. Liposomal bupivacaine (Exparel, Pacira Pharmaceuticals, Inc.) was added to the drug formulary at Ochsner Medical Center in February 2012, and intravenous (IV) acetaminophen (Ofirmev, Mallinckrodt Pharmaceuticals) and IV ibuprofen (Caldolor, Cumberland Pharmaceuticals, Inc.) were added shortly thereafter. To assess the clinical and economic impact of these medications, we conducted a medical record review of patients who underwent colorectal surgery before and after the introduction of these drugs.

METHODS

We conducted a retrospective medical record review of consecutive patients undergoing major colorectal surgery from October 2011 to January 2013. All procedures were performed by a board-certified colorectal surgeon with a colorectal resident or general surgery chief resident. Procedures varied from laparoscopic ileocolic resections

Table 1. Patient Demographics

Characteristic	Multimodal Pain Management Group (n=66)			Conventional Pain Management Group (n=167)			*P* Value
Average age, years	59.8			54.7			>0.05
Male sex	39.4%			46.1%			>0.05
Laparoscopic cases	25.8%			25.1%			>0.05
Procedure	**Open**	**Laparoscopic**	**Total**	**Open**	**Laparoscopic**	**Total**	
Ileocolic resection and right colon resection, n (%)	16 (24)	9 (14)	25 (38)	29 (17)	20 (12)	49 (29)	>0.05
Left, sigmoid, and total colectomy, n (%)	19 (29)	6 (9)	25 (38)	52 (31)	14 (8)	66 (40)	>0.05
Low anterior resection, total colectomy, and proctectomy, n (%)	14 (21)	2 (3)	16 (24)	44 (26)	8 (5)	52 (31)	>0.05

to low anterior resection, most with diversion. Patient inclusion criteria were age >18 years, a hospital stay duration ≥72 hours and ≤30 days, and admission during the study period. Patients were excluded from this study if they received an anorectal procedure or minor operations such as ileostomy closure or hernia repairs, their postoperative record lacked a pain scale, or they did not meet the inclusion criteria. During the study period, all patients were managed using standard enhanced recovery pathways.

Prior to the 2012 addition of liposomal bupivacaine to the Ochsner formulary, surgeons relied on opioid medications for postoperative pain management. There was a variable practice pattern between infiltration of short-duration local anesthetics and no local anesthetic.

Patients who received a single dose of 266 mg liposomal bupivacaine via surgical site infiltration at the end of surgery along with 1,000 mg of IV acetaminophen every 6 hours and 800 mg of IV ibuprofen every 6 hours were compared with patients who received conventional pain management techniques in colorectal surgery. When patients resumed oral intake, the administration of acetaminophen and ibuprofen was stopped or the IV administration was converted to an oral form. During the study, the liposomal bupivacaine was diluted with 20-120 cc of saline and injected in cc aliquots at multiple sites along the incision into the space between the peritoneum and posterior rectus abdominis muscle (below the umbilicus) and transversalis fascia (above the umbilicus) as well as the subdermal space.

Data were obtained from patient medical records that included demographics; length of hospital stay; postoperative pain scores using a 10-point visual pain scale; the total dose of opioids consumed at time intervals 12, 24, 36, 48, 60, and 72 hours in morphine equivalents; the time to first opioid request; and the quantity of medications used to mitigate opioid-related adverse events. The study was conducted by the authors at Ochsner Medical Center and approved by the hospital institutional review board. Data were statistically analyzed by using *t* test and chi-square analysis with StatView (SAS Institute Inc.), and $P<0.05$ was considered significant.

RESULTS

A total of 233 patients were included in this study. Of these, 66 patients received postsurgical multimodal pain management, and 167 received conventional pain management treatment. Patient demographics are summarized in Table 1, and results are presented in Table 2. The average postoperative pain score using the 10-point visual pain scale was 5.5 for the multimodal group and 6.6 for the conventional group ($P<0.05$). The medians were 6 and 8, respectively. Patients in the multimodal group received their first dose of opioid medications approximately 5.2 hours (SD=3.3) after the conclusion of their surgery, while patients in the conventional group required opioid medications approximately 2.9 hours (SD=3.2) after their procedures ($P<0.05$). The postoperative length of stay in the multimodal group averaged 7.2 days, compared to 9.0 days in the conventional group ($P=0.04$).

Patients in the multimodal group required less cumulative opioid medication at the 12-, 24-, 36-, 48-, 60-, and 72-hour time intervals (Figure). At 72 hours, patients in the multimodal group required an average of 38.96 mg (SD=62.1) of IV morphine equivalents, and patients in the

Table 2. Postoperative Results by Treatment Group

	Multimodal Pain Management Group (n=66)	Conventional Pain Management Group (n=167)	*P* Value
Postoperative pain scores, 0-10			
Average	5.5	6.6	<0.05
Median	6	8	<0.05
Opioid-free hours			<0.05
Average	5.2	2.9	
SD	3.3	3.2	
Postoperative hospital stay, days			0.04
Average	7.2	9.0	
Range	2-32	2-81	

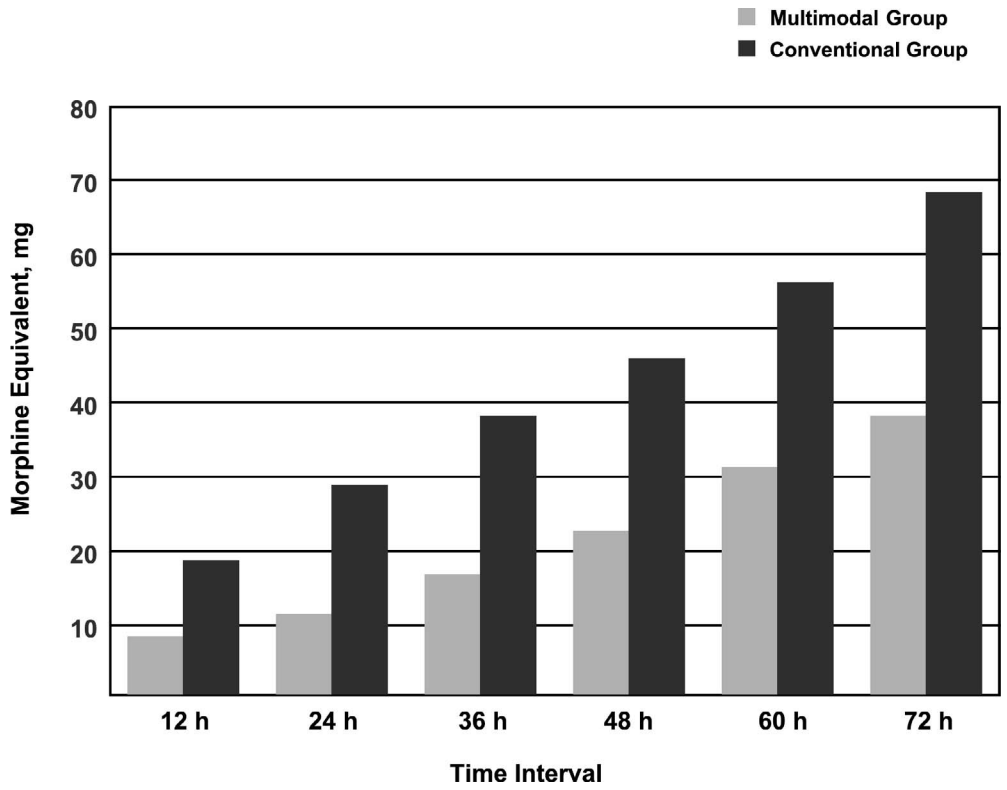

Figure. Cumulative postoperative narcotic use ($P<0.03$).

conventional group required an average of 68.33 mg (SD=117.9) of IV morphine equivalents (P=0.03).

The quantity of medications administered to mitigate opioid-related adverse effects was also tracked (Table 3). These drugs included antipruritic medications (diphenhydramine, hydroxyzine, and nalbuphine), antiemetic medications (promethazine, ondansetron, metoclopramide, droperidol, and haloperidol), and anticonstipation medications (docusate, sennosides, lactulose, polyethylene glycol, and bisacodyl). Compared to patients receiving conventional pain management regimens, patients in the multimodal group required significantly less antipruritic medication, 0.4 vs 4.5 doses (P=0.03); antiemetic medication, 2.7 vs 6.7 doses (P=0.01); and anticonstipation medication, 0.6 vs 0.9 doses (P=0.05).

Table 3. Average Number of Doses of Medication Used to Treat Opioid-Related Adverse Events

	Multimodal Pain Management Group (n=66)	Conventional Pain Management Group (n=167)	*P* Value
Antipruritic medication	0.4	4.5	0.03
Antiemetic medication	2.7	6.7	0.01
Anticonstipation medication	0.6	0.9	0.05

In the multimodal group, 17 patients (25.8%) had laparoscopic procedures, and 49 patients (74.2%) had open procedures. In the conventional group, 42 patients (25.1%) had laparoscopic procedures, and 125 patients (74.9%) had open procedures. Subgroup analysis compared laparoscopic to open procedures within the multimodal and conventional pain management groups. Patients in the multimodal group needed less opioid use and experienced fewer opioid-related adverse events, demonstrating the efficacy of multimodal pain management.

DISCUSSION

Care of the postoperative patient has changed significantly in recent years. Components of this care have been grouped into the Enhanced Recovery After Surgery (ERAS) care pathways.[8] These care pathways have improved the patient experience, significantly shortened the postoperative hospital stay, and hastened a return to activity and work.[8] The management of postoperative pain is a major factor in patient care. In initial studies, thoracic epidurals were used to minimize pain and reduce the need for narcotic medication.[9] However, thoracic epidurals are invasive and resource intensive, have variable effectiveness, and often require a urinary catheter.

The multimodal pain management regimen in this study used several new medication formulations (ie, liposomal bupivacaine, IV acetaminophen, and IV ibuprofen). Liposomal bupivacaine is an extended-release formulation of bupivacaine, an amide local anesthetic that provides prolonged postsurgical analgesia with a single administration into the surgical site at the end of the procedure.[10] Bupivacaine is released from the multivesicular liposome during a period of time, resulting in prolonged plasma levels

and analgesia for 72 hours, with a corresponding reduction in the use of opioids. In a study comparing the efficacy of liposomal bupivacaine (266 mg) and bupivacaine (75 mg) administered for postsurgical analgesia, liposomal bupivacaine was associated with statistically significant lower cumulative pain scores at 72 hours, delayed and lower consumption of opioids, and fewer opioid-related adverse events compared to bupivacaine.[11]

The liposomal formulation of bupivacaine produces a controlled delivery that results in a higher potency and reduced toxicity compared to the standard formulation.[12] In studies of postoperative pain, liposomal bupivacaine resulted in better pain control and a decreased need for opioids compared to other bupivacaine formulations and placebo.[13,14] Additional adjuvants such as acetaminophen (which acts centrally) and ibuprofen (which acts at multiple sites in the pain pathway) assist with analgesia and reduce opioid needs. Improved postsurgical pain control is a vital component of optimal patient care because it assists in recovery by shortening hospital stays and allowing for faster mobilization, thereby reducing overall healthcare costs.[13]

Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen are useful for reducing the amount of opiates requested by and administered to the patient, thus reducing opioid-related side effects.[15] They are useful for treating mild to moderate levels of pain. NSAIDs act by inhibiting the enzyme cyclooxygenase and thereby blocking the production of prostaglandins, resulting in an antiinflammatory response.

Acetaminophen is a centrally acting analgesic, but it lacks peripheral antiinflammatory effects. Oral acetaminophen is widely administered for acute pain relief and is a common ingredient in many combination oral pain medications. Patients must not exceed the 4,000 mg daily maximum dose of acetaminophen because of the risk of hepatotoxicity. Systematic reviews of randomized controlled trials confirm the efficacy of oral acetaminophen for acute pain.[16] However, oral acetaminophen has a slow onset of analgesia, and the lack of a parenteral form has limited its use in the immediate postoperative period. A stable IV form of acetaminophen is now commercially available. Acetaminophen's major advantages over NSAIDs are its lack of interference with platelet function and its safe administration in patients with a history of peptic ulcers or asthma. Opioid-sparing effects have been associated with acetaminophen administered intravenously.[17] A systematic review identified 21 studies comparing acetaminophen alone or in combination with NSAIDs and reported increased efficacy with the combination of the 2 agents than with either alone.[18]

Our study showed that multimodal pain management after major colorectal surgery results in significantly lower pain scores, decreased opioid use, fewer opioid-related adverse effects, and decreased postoperative length of stay (7.2 vs 9.0 days). In evaluating medications used to treat the opioid-related adverse effects, specifically pruritus, nausea and vomiting, and constipation, it was not surprising that the patients who received fewer opioids had fewer adverse effects that are commonly associated with opioids.

In addition to evaluating the effectiveness of a new therapy or drug, the cost must also be evaluated. The costs of drugs are often allocated to a pharmacy cost center, and the offsetting benefits are not often compared. This silo management often hinders the introduction of new medications. Liposomal bupivacaine is a new pharmacokinetic design associated with a higher cost compared to local anesthetics that have been on the market for decades. Liposomal bupivacaine costs approximately $280-$300 per 266 mg vial, and other adjuvants such as IV acetaminophen ($120 per day) and IV ibuprofen ($40 per day), as well as pharmacy and nursing costs, can cause concerns and hinder hospital formulary inclusion. Patients receiving these medications were expected to have higher pharmacy costs, and this study was conducted in part to support the process of new drug acquisition for multimodal pain management at our institution.

The overall shorter length of stay in the multimodal group (7.2 vs 9.0 days) resulted in the opening of additional beds at our institution. The 66 patients in the multimodal group averaged 1.82 fewer hospital days, clearing approximately 120 additional bed days during the study period. Increasing bed availability is crucial in a busy institution such as Ochsner that often has near-total occupancy.

This study has several limitations. First, we did not research the underlying disease states and home medications of the patients. Thus, underlying conditions such as chronic pain were not considered when we analyzed the total dosage of opioids and drugs that were administered to mitigate adverse effects. Second, the researchers were unable to distinguish the exact cause of adverse effects such as pruritus, nausea, vomiting, and constipation. Finally, the groups were not controlled for disease processes, operative procedures, and comorbidities.

Despite these limitations, the adoption of multimodal pain management led to significant improvements in patient care. This study supports the adoption of this type of pain management in our postoperative care pathways.

CONCLUSION

Patients receiving multimodal pain management during and after major colorectal surgeries had lower initial pain scores, delayed administration of postoperative opioids, decreased total dosage of opioids at various intervals up to 72 hours, and decreased hospital lengths of stay. Patients in the multimodal group had a decrease in average length of stay that aided in bed availability at our institution. Our experience supports the use of multimodal pain management in patients undergoing colorectal surgery. Multimodal pain management including liposomal bupivacaine has become a standard part of our postoperative care pathways.

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