



Risk factors for complications and return to the emergency department after interscalene block using liposomal bupivacaine for shoulder surgery

Ajith Malige, MD^{a,*}, Shawn Yeazell, MD^a, Anna Ng-Pellegrino, MD^b, Gregory Carolan, MD^a

^aDepartment of Orthopaedic Surgery, St. Luke's University Health Network, Bethlehem, PA, USA

^bDepartment of Anesthesia, St. Luke's University Health Network, Bethlehem, PA, USA

Background: Exparel (liposomal bupivacaine) has recently gained favor for use in interscalene regional blocks for shoulder surgery. While effective for pain relief, this does have adverse effects that can lead to postoperative emergency department (ED) visits. This study aimed to identify any patient risk factors that are associated with complications leading to ED return visits owing to interscalene blocks using Exparel before shoulder surgery.

Methods: A retrospective chart review was performed for all patients undergoing shoulder surgery with an Exparel interscalene block in an 8-month period. For each patient, demographic information, comorbidities, type of block, postoperative complications, ED return visits, and readmissions were recorded. The 5-factor modified Frailty Index score and the Charlson Comorbidity Index score were calculated. Univariate and multivariate logistic regressions were conducted to identify risk factors associated with increased complications and return to the ED.

Results: Overall, 352 patients were included; most patients were men, were aged between 51 and 70 years, and had a body mass index of 25.0–35.0. Postoperative complications related to the Exparel interscalene block occurred in 58 patients (16.5%), including 37 minor complications (10.5%) and 21 major complications (6.0%) that led to return ED visits. Univariate analysis yielded American Society of Anesthesiologists (ASA) score ($P = .03$) as a significant predictor of minor complications. Multivariate logistic regression analysis yielded ASA score ($P = .096$; odds ratio, 1.64) as trending toward being a significant risk factor for minor complications. Univariate analysis yielded age ($P = .006$), ASA score ($P = .009$), and Charlson Comorbidity Index score ($P = .002$) as significant predictors of major complications. Multivariate logistic regression analysis yielded ASA score ($P = .049$; odds ratio, 2.25) as the only significant risk factor for major complications.

Conclusion: Surgeons and anesthesiologists should strongly consider a patient's ASA score, in addition to his or her pulmonary and cardiac history, when deciding whether the patient is an appropriate candidate for an interscalene regional block using Exparel for shoulder surgery.

Level of evidence: Level IV; Case Series; Treatment Study

© 2020 Journal of Shoulder and Elbow Surgery Board of Trustees. All rights reserved.

Keywords: Exparel; liposomal; bupivacaine; interscalene; shoulder; complications

Institutional review board (IRB) approval was obtained from both the St. Luke's University Health Network IRB Committee and the Temple University School of Medicine IRB Committee.

*Reprint requests: Ajith Malige, MD, Department of Orthopaedic Surgery, St Luke's University, 801 Ostrum St, Bethlehem, PA 18015, USA.
E-mail address: ajith.malige@gmail.com (A. Malige).

Postoperative pain can have far-reaching effects on patient recovery, functional status, and overall satisfaction. Orthopedic postoperative pain, in particular, has been documented as one of the hardest types of pain to control.¹² Because of this, surgeons and anesthesiologists have turned to preoperative regional nerve blocks in hopes of providing pain relief and decreasing opioid use postoperatively. Whereas multiple regional blocks have been proposed and used to provide postoperative analgesia after shoulder surgery, interscalene regional blocks have become the standard of care in most locations.^{1,23}

Interscalene blocks provide predictable sensory anesthesia to the C4-C7 nerve roots and at times including the C3 nerve root while sparing C8 and T1.³³ The ideal anesthetic agent for interscalene blocks would provide long-lasting pain control with minimal side effects. Recently, liposomal bupivacaine injectable suspension (Exparel; Pacira BioSciences, Parsippany, NJ, USA) has gained US Food and Drug Administration approval for interscalene block, and its use in shoulder surgery has increased rapidly.⁸ The liposomal formulation of Exparel allows for an extended delivery of medication to specific targets while theoretically decreasing systemic toxicity.²⁸ However, physicians must be aware of and monitor for the pharmacologic side effects of Exparel, including nausea, vomiting, and pruritus,^{9,15} and complications associated with the technical aspects of interscalene nerve blocks, including brachial plexus injury, dyspnea due to phrenic nerve involvement, and subsequent ipsilateral hemidiaphragmatic paralysis, as well as pneumothorax.^{3,18}

Although the clear benefits (in decreasing pain scores and opioid use postoperatively) as well as side-effect profiles of interscalene blocks using Exparel are well documented,^{19,22,27} risk factors for adverse events using this local anesthetic for interscalene blocks have not been studied. This study aimed to identify any patient-specific risk factors that are associated with patient-reported adverse events (minor complications) and adverse events requiring emergency department (ED) visits (major complications) or hospital admissions owing to interscalene blocks using Exparel as a regional anesthetic for open and arthroscopic shoulder surgery. We believe that specific patient comorbidities, most notably cardiopulmonary conditions, are associated with a higher incidence of minor and major complications after interscalene blocks using Exparel.

Materials and methods

This retrospective chart review was conducted within an academic suburban hospital health network. All patients who underwent open or arthroscopic shoulder surgery over an 8-month period were reviewed. Patients were included in our study if they received a preoperative ultrasound-guided interscalene block using Exparel and subsequently underwent general anesthesia for the surgical procedure. Any patients who received other types of

upper-extremity blocks or received blocks not using Exparel, as well as those who had missing chart information, were excluded from this study.

With the patient in a reclined position, the interscalene block was performed by an anesthesiologist experienced in regional anesthesia administration. The neck was tilted toward the contralateral side of the block site. With ultrasound guidance,⁴ landmarks were found that showed the C5-C7 nerve roots as part of the brachial plexus. A 5.08-cm (2-inch) Stimuplex echogenic needle (B. Braun Medical, Bethlehem, PA, USA) was used to deposit anesthetic mixture just beyond the middle scalene muscle while trying to avoid spread toward the anterior scalene muscle to limit phrenic nerve paralysis. The amount of anesthetic used was decided by each anesthesiologist based on patient, surgery, and preference. All patients underwent the surgical procedure using a general anesthetic.

For each patient, demographic information (age, sex, and body mass index), comorbidities (pulmonary conditions, congestive heart failure [CHF], smoking history, and American Society of Anesthesiologists [ASA] score), type of block using Exparel and 0.5% bupivacaine (Exparel volume and total volume), and postoperative complications were recorded. Charts were reviewed for complications reported by the patient through patient phone calls, during ED visits, or at the first postoperative follow-up appointment. Minor complications were defined as patient-reported symptoms for which the patient did not return to the ED for further evaluation, whereas major complications were defined as symptoms that led to a return ED visit for further evaluation. The 5-factor modified Frailty Index (mFI-5) score²⁴ and the Charlson Comorbidity Index (CCI) score²⁹ were calculated for each patient as well. Univariate analyses (χ^2 test, Fisher exact test, and independent *t* test as appropriate) and multivariate logistic regression analyses (IBM SPSS Statistics for Windows, version 23; IBM, Armonk, NY, USA) were conducted to identify any risk factors associated with an increased complication rate and return to the ED. For all analyses, $P \leq .05$ denoted statistical significance, with no adjustment for multiple comparisons.

Results

Overall, 352 patients treated by 5 surgeons and 26 anesthesiologists were included in our study. Most of our patients were men ($n = 202$, 57.4%), were aged between 51 and 70 years ($n = 197$, 56.0%), and had a body mass index between 25 and 35 ($n = 219$, 62.2%). Arthroscopic shoulder surgery was performed in 269 patients (76.4%), whereas open surgical procedures were performed in 83 (23.6%) (Table I). Of the surgical procedures, 281 (79.8%) were outpatient procedures, mostly arthroscopic operations, whereas 71 (20.2%) were inpatient procedures, mostly shoulder arthroplasties. In total, 95.2% of patients ($n = 335$) were undergoing their first ipsilateral shoulder surgery. Postoperative complications occurred after the Exparel interscalene block in 58 patients (16.5%). These patients most commonly complained of dyspnea and chest pain ($n = 44$, 12.5%), with 41 patients complaining of dyspnea and 3 complaining of chest pain. In addition, 6 patients (1.7%) reported superficial reactions such as

Table I Demographic breakdown of sample population

	Sex, n (%)		Total, n (%)
	Male	Female	
Age			
≤30 yr	22 (6.3)	5 (1.4)	27 (7.7)
31-50 yr	35 (9.9)	26 (7.4)	61 (17.3)
51-70 yr	116 (33.0)	81 (23.0)	197 (56.0)
≥71 yr	29 (8.2)	38 (10.8)	67 (19.0)
BMI			
≤25.0	31 (8.8)	28 (8.0)	59 (16.8)
25.1-30.0	68 (19.3)	47 (13.4)	115 (32.7)
30.1-35.0	61 (17.3)	43 (12.2)	104 (29.5)
≥35.1	42 (11.9)	32 (9.1)	74 (21.0)
Type of surgery			
Arthroscopic	159 (45.2)	110 (31.2)	269 (76.4)
Open	43 (12.2)	40 (11.4)	83 (23.6)
Total	202 (57.4)	150 (42.6)	352 (100.0)

BMI, body mass index.

swelling, dermatitis, and superficial hematoma. Minor complications were noted in 37 patients (10.5%), whereas 21 patients (6.0%) had major complications and returned to the ED for further workup of their complications at an average of 4.5 days after surgery. Within the latter group, 12 patients (3.4%) were subsequently readmitted (Table II). These patients were all provided supportive care and observed until being deemed medically safe for discharge within the first week.

Univariate analysis of minor complications due to the interscalene block using Exparel yielded ASA score ($P = .003$) as a significant predictor, with CHF ($P = .07$) trending toward being a significant predictor (Figs. 1-3). Multivariate logistic regression analysis ($P = .43$, Hosmer-Lemeshow test) yielded ASA score ($P = .096$; odds ratio, 1.64) as trending toward being a significant risk factor for minor complications (Table III).

Univariate analysis of risk factors for major complications (return to the ED for further workup) yielded age ($P = .006$), ASA score ($P = .009$), and CCI score ($P = .002$) as significant predictors, with pulmonary history ($P = .060$) trending toward being a significant risk factor (Figs. 1-3). Multivariate logistic regression analysis ($P = .91$, Hosmer-Lemeshow test) yielded ASA score ($P = .049$; odds ratio, 2.25) as the only statistically significant risk factor for return to the ED (Table IV).

Discussion

Liposomal extended-release bupivacaine (Exparel) has been shown to provide effective postoperative pain control in both orthopedic and non-orthopedic procedures.^{19,22,27,30} Its liposomal encapsulation allows for delivery of the medication over an extended period, without having to reach toxic plasma or systemic levels. However, the long-

acting nature of this anesthetic potentially increases the chances of side effects associated with this medication and interscalene blocks in general. Although patients are overall happy with the pain relief they receive and minimal side effects they experience when Exparel is used in an interscalene block,^{16,17,19,22,27} physicians and patients should continuously watch out for the complications associated with both interscalene blocks and Exparel, especially because Exparel is a longer-acting anesthetic.

Our overall complication rate of 16.5% is much higher than the complication rates documented in the literature after interscalene blocks^{2,13} but similar to rates documented after use of Exparel.^{9,31} These higher rates are most likely related to the extended-release and longer-lasting properties of this medication, continuing to provide pain relief but also yielding the opportunity for unintended side effects. However, it should be noted that most of these complications were not significant, as only 6% of patients felt the need to present to the ED for evaluation of major complications.

The most common complication in our cohort was cardiopulmonary in nature, with patients presenting with complaints of shortness of breath and chest pain. Although these patients received a full workup of their symptoms looking for identifiable causes such as pulmonary embolism if the symptoms did not subside, one must consider the effects of an interscalene block on pulmonary function. By blocking the C5-C7 nerve roots, as well as including C3 and C4 at times, this block is known to affect ipsilateral phrenic nerve function, causing ipsilateral hemidiaphragmatic paralysis and decreased forced vital capacity.^{25,26} In patients who already have compromised cardiopulmonary function, an added decrease in pulmonary function and movement of air through the pulmonary tree can cause an increased need for work of breathing to continue to deliver oxygen to the body, resulting in shortness of breath and sometimes chest pain. Although these effects were not seen in the pilot study of interscalene blocks using Exparel,¹⁷ these adverse reactions have been documented in the literature after interscalene blocks using all types of local anesthetic medication,^{25,26} so it should be of no surprise that these effects would be seen using Exparel.

Other complications observed included a superficial reaction, seen in 1.7% of patients, an adverse reaction associated with all injections and blocks, and nausea and vomiting, seen in 2 patients (0.6%), a documented side effect of Exparel.⁹ However, nausea and vomiting can also be a result of the general anesthetic, making it difficult to isolate Exparel as their cause. Three patients also showed symptoms of transient Horner syndrome,^{7,21} a possible complication after an interscalene block owing to paralysis of the ipsilateral sympathetic chain (stellate ganglion) or hematoma around this area. Just as with cardiopulmonary adverse events, Horner syndrome was not seen in the pilot study on Exparel interscalene blocks¹⁶ but is a documented adverse reaction after interscalene blocks using any local anesthetic medications.^{25,26}

Table II Patients with total, minor, and major complications after Exparel interscalene block

Complication	Total patients, n (%)	Minor complications, n (%)	Major complications, n (%)
Dyspnea and chest pain	44 (12.5)	28 (8.0)	16 (4.5)
Superficial or skin reaction	6 (1.7)	2 (0.6)	4 (1.1)
Horner syndrome	3 (0.9)	3 (0.9)	0 (0.0)
Nausea or vomiting	2 (0.6)	2 (0.6)	0 (0.0)
Multiple or other	3 (0.9)	2 (0.6)	1 (0.3)
Total	58 (16.5)	37 (10.5)	21 (6.0)

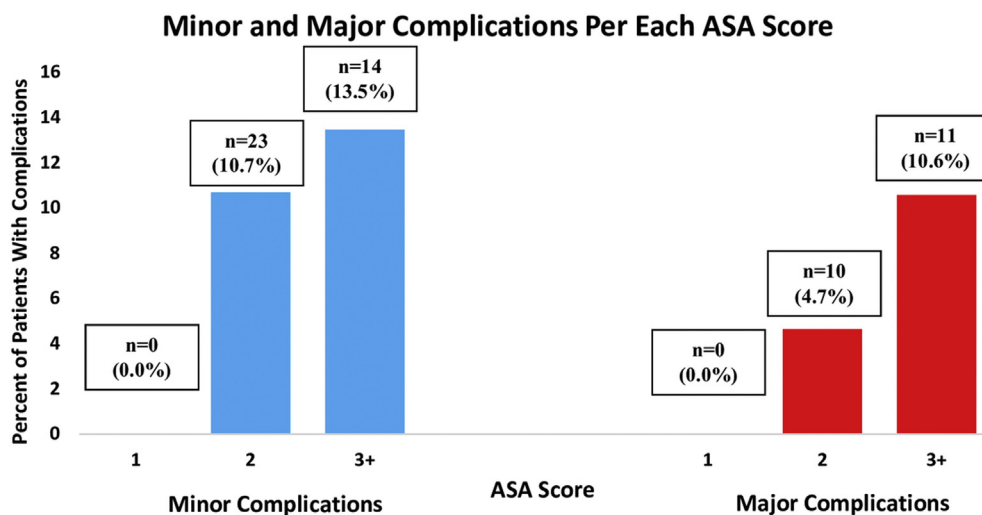


Figure 1 Complications and return to emergency department per each American Society of Anesthesiologists (ASA) score.

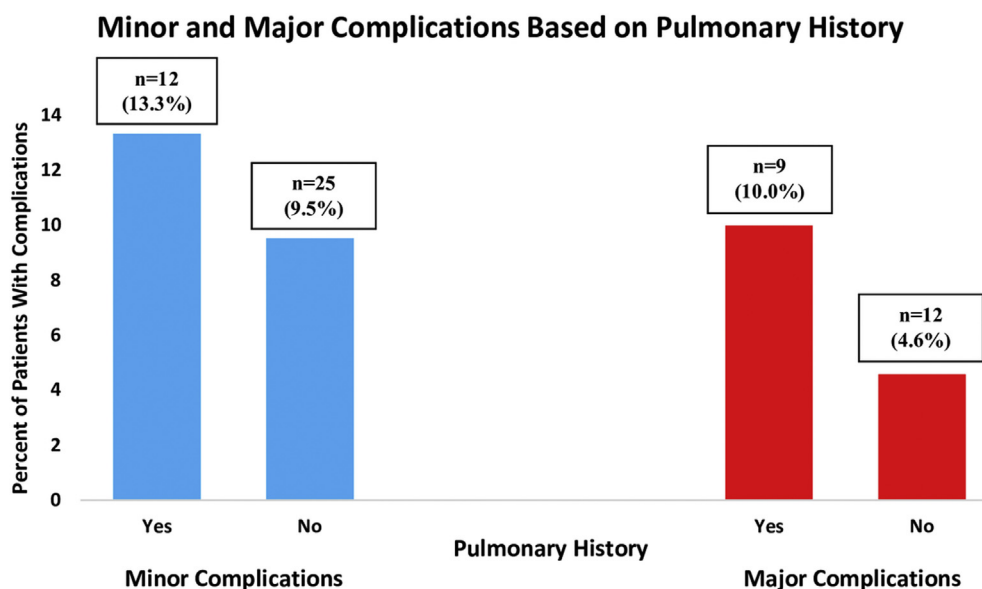


Figure 2 Complications and return to emergency department based on pulmonary history.

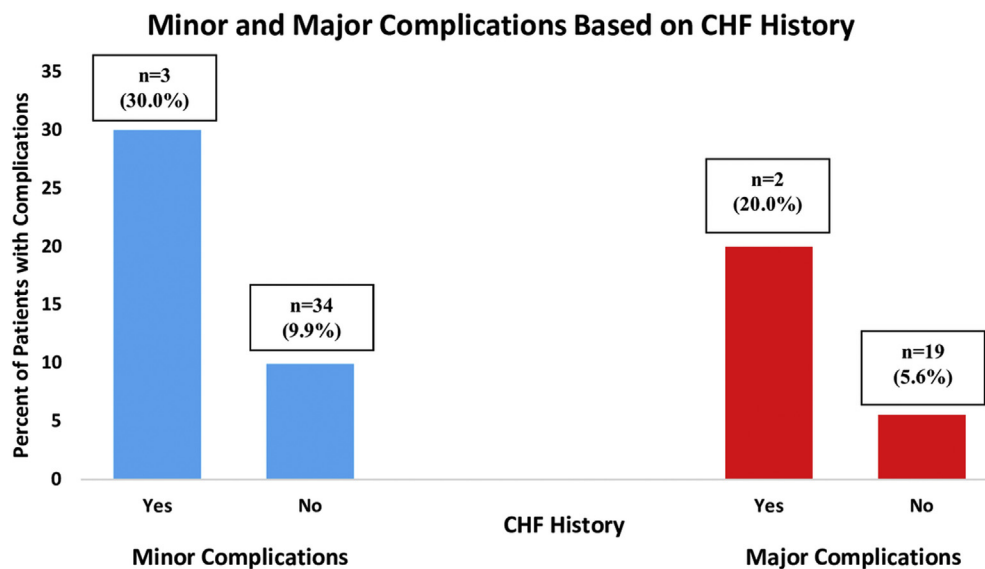


Figure 3 Complications and return to emergency department based on congestive heart failure (*CHF*) history.

Table III Statistical analysis of risk factors for minor complication rate

	<i>P</i> value	
	Univariate analysis	Multivariate Logistic regression
Age	.520	NA
BMI	.140	NA
Pulmonary history	.42	NA
CHF	.07	.191
Smoking history	.181	NA
ASA score	.003	.096
Expirel volume	.660	NA
Total volume	.660	NA
mFI-5	.510	NA
CCI	.530	NA

BMI, body mass index; *NA*, not applicable; *CHF*, congestive heart failure; *ASA*, American Society of Anesthesiologists; *mFI-5*, 5-factor modified Frailty Index; *CCI*, Charlson Comorbidity Index.

Age, BMI, ASA score, Expirel volume, total volume, mFI-5 score, and CCI score were analyzed using the unequal-variance *t* test. Pulmonary history and smoking status were analyzed using the χ^2 test. CHF history was analyzed using the Fisher exact test.

Table IV Statistical analysis of risk factors for return to emergency department

	<i>P</i> value	
	Univariate analysis	Multivariate Logistic regression
Age	.006	.248
BMI	.120	NA
Pulmonary history	.060	.182
CHF	.110	NA
Smoking history	.740	NA
ASA score	.009	.049
Expirel volume	.660	NA
Total volume	.790	NA
mFI-5	.460	NA
CCI	.002	.467

BMI, body mass index; *NA*, not applicable; *CHF*, congestive heart failure; *ASA*, American Society of Anesthesiologists; *mFI-5*, 5-factor modified Frailty Index; *CCI*, Charlson Comorbidity Index.

Age, BMI, ASA score, Expirel volume, total volume, mFI-5 score, and CCI score were analyzed using the unequal-variance *t* test. Pulmonary history and smoking status were analyzed using the χ^2 test. CHF history was analyzed using the Fisher exact test.

The ASA score, a measure of systemic disease, was the strongest predictor of both minor and major complications. Whereas no patient with an ASA score of 1 had any minor or major complications, patients were 1.64 times more likely to have minor complications and 2.25 times more likely to return to the ED for workup of a major complication for every point increase in the ASA score. This

correlation between a higher ASA score and the complication rate is common in both orthopedic and non-orthopedic surgical procedures.^{6,11} It is interesting to note, however, that Johnson et al¹⁰ found that an increased ASA score was associated with increased surgical but not medical complications, a finding that is not echoed in our previously stated studies.^{6,11} In addition, CHF history and

age were predictors of minor and major complications, respectively, only in univariate analysis. Finally, although a pulmonary history was also only a significant risk factor for major complications in univariate analysis, all 3 factors (increasing age, CHF history, and pulmonary history) should still be considered individually in identifying patients at risk of complications after an Exparel interscalene block. As discussed before, any patient with decreased cardiopulmonary reserve, which occurs in elderly patients and patients with cardiopulmonary comorbidities, can experience symptom exacerbation due to a prolonged interscalene block that can paralyze the phrenic nerve and decrease pulmonary function.

Surprisingly, smoking status, with both current and previous smokers included, was not associated with minor or major complications, despite the known decrease in pulmonary function at baseline in these patients. Moreover, Exparel volume and total volume of the block when Exparel was mixed with 0.5% bupivacaine were both surprisingly not significant predictors of either outcome. A decreased block volume has been shown to decrease complications after interscalene blocks.^{14,18} However, the long-lasting effects of Exparel might mitigate these differences in volume, causing complications at any volume. This might suggest that the accuracy of the placement of medication, which can be enhanced by ultrasound use,¹⁴ is more important than the volume used regarding minimizing adverse effects. Finally, the CCI score, a documented predictor of 30-day mortality,¹⁶ was significant only in univariate analysis for major complications, whereas the mFI-5 score^{5,24,20,32} was not predictive of either minor or major complications. Although both factors include a cardiopulmonary history in their assessment and the CCI score additionally takes into account a patient's age, both overall scores did not strongly predict minor complications, whereas the CCI score only predicted major complications, probably owing to the other factors included. Both results are surprising, especially given that many studies have documented the mFI-5 score's ability to predict risk factors in multiple orthopedic and non-orthopedic settings.

The results of this study have placed a greater emphasis on multidisciplinary decision making, communication, and patient education in our practice. Our senior author discusses all patients with the anesthesiology team, deciding which patients are good candidates for an Exparel block. Given the fact that our study mimicked other studies in showing a very low rate of long-term side effects from the block (our study had none), all patients who are medically cleared to receive the block are offered it preoperatively. A detailed discussion is had with every patient about all possible side effects associated with this block, what to expect postoperatively, and what the patient can do to help relieve his or her symptoms. Patients at high risk of major or minor complications, per our results, are made aware of this fact before deciding whether they want the block. Our hope is that this early education will help relieve patient concerns and unnecessary trips to the ED. Any patient who

does not receive the block is provided pain control using a multimodal analgesia plan.

Limitations

The limitations of our study are those inherent to all retrospective chart reviews, including sampling bias and dependence on physician charting. Although our study did include 5 surgeons operating in 5 locations, further studies should include larger cohorts from more varied patient populations. Furthermore, the effectiveness of any block is performer dependent. Although we did not analyze complications by anesthesiologist, no anesthesiologist had >14 complications (26.4%) or a complication rate of 33.3% (1 of 3 patients). Whereas the lack of a nonstandardized anesthesiology team brings variability to our data, this is representative of a true clinical setting in which multiple providers are performing these blocks. Finally, there is limited comparable research on complication rates and risk factors after liposomal bupivacaine or even interscalene blocks in the literature with which to compare our results.

Conclusion

We have identified ASA score, increasing age, pulmonary history, CHF history, and CCI score as possible predictive risk factors for postoperative minor and major complications after shoulder surgery using Exparel interscalene blocks. Although all patients should be educated about the benefits and possible side effects of Exparel interscalene blocks, physicians should spend extra time discussing these symptoms, as well as what to expect postoperatively, with patients with these risk factors. In addition, surgeons and anesthesiologists should strongly consider the risk factors for major complications when deciding whether a patient is a good candidate for an interscalene block using Exparel before shoulder surgery.

Disclaimer

Gregory Carolan reports relations with DePuy Mitek, Wright Medical Group, Aesculap, and *Arthroscopy: The Journal for Arthroscopic and Related Surgery*. All the other authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

References

1. Auyong DB, Hanson NA, Joseph RS, Schmidt BE, Slee AE, Yuan SC. Comparison of anterior suprascapular, supraclavicular, and interscalene nerve block approaches for major outpatient arthroscopic

- shoulder surgery: a randomized, double-blind, noninferiority trial. *Anesthesiology* 2018;129:47-57. <https://doi.org/10.1097/ALN.0000000000002208>
2. Bishop JY, Sprague M, Gelber J, Krol M, Rosenblatt MA, Gladstone J, et al. Interscalene regional anesthesia for shoulder surgery. *J Bone Joint Surg Am* 2005;87:974-9. <https://doi.org/10.2106/JBJS.D.02003>
 3. Borgeat A, Ekatothramis G, Kalberer F, Benz C. Acute and nonacute complications associated with interscalene block and shoulder surgery: a prospective study. *Anesthesiology* 2001;95:875-80.
 4. Chan VW. Applying ultrasound imaging to interscalene brachial plexus block. *Reg Anesth Pain Med* 2003;28:340-3. [https://doi.org/10.1016/s1098-7339\(03\)00189-5](https://doi.org/10.1016/s1098-7339(03)00189-5)
 5. Chimukangara M, Helm MC, Frelich MJ, Bosler ME, Rein LE, Szabo A, et al. A 5-item frailty index based on NSQIP data correlates with outcomes following paraesophageal hernia repair. *Surg Endosc* 2017;31:2509-19. <https://doi.org/10.1007/s00464-016-5253-7>
 6. Cullen DJ, Apolone G, Greenfield S, Guadagnoli E, Cleary P. ASA physical status and age predict morbidity after three surgical procedures. *Ann Surg* 1994;220:3.
 7. Ekatothramis G, Macaire P, Borgeat A. Prolonged Horner syndrome due to neck hematoma after continuous interscalene block. *Anesthesiology* 2001;95:801-3.
 8. Hannan CV, Albrecht MJ, Petersen SA, Srikumaran U. Liposomal bupivacaine vs interscalene nerve block for pain control after shoulder arthroplasty: a retrospective cohort analysis. *Am J Orthop (Belle Mead NJ)* 2016;45:424-30.
 9. Ilfeld BM, Viscusi ER, Hadzic A, Minkowitz HS, Morren MD, Lookabaugh J, et al. Safety and side effect profile of liposome bupivacaine (Exparel) in peripheral nerve blocks. *Reg Anesth Pain Med* 2015;40:572-82. <https://doi.org/10.1097/AAP.0000000000000283>
 10. Johnson CC, Sodha S, Garzon-Muvdi J, Petersen SA, McFarland EG. Does preoperative American Society of Anesthesiologists score relate to complications after total shoulder arthroplasty? *Clin Orthop Relat Res* 2014;472:1589-96. <https://doi.org/10.1007/s11999-013-3400-1>
 11. Kastanis G, Topalidou A, Alpantaki K, Rosiadi M, Balalis K. Is the ASA score in geriatric hip fractures a predictive factor for complications and readmission? *Scientifica (Cairo)* 2016;2016:7096245. <https://doi.org/10.1155/2016/7096245>
 12. Kehlet H, Wilkinson RC, Fischer HB, PROSPECT Working Group. PROSPECT: evidence-based, procedure-specific postoperative pain management. *Best Pract Res Clin Anaesthesiol* 2007;21:149-59. <https://doi.org/10.1155/2016/7096245>
 13. Lenters TR, Davies J, Matsen FA III. The types and severity of complications associated with interscalene brachial plexus block anesthesia: local and national evidence. *J Shoulder Elbow Surg* 2007;16:379-87. <https://doi.org/10.1016/j.jse.2006.10.007>
 14. Maalouf DB, Dorman SM, Sebeo J, Goytizolo EA, Gordon MA, Yadeau JT, et al. Prospective, randomized double-blind study: does decreasing interscalene nerve block volume for surgical anesthesia in ambulatory shoulder surgery offer same-day patient recovery advantages? *Reg Anesth Pain Med* 2016;41:438-44. <https://doi.org/10.1097/AAP.00000000000000418>
 15. Marcet JE, Nfonsam VN, Larach S. An extended pain relief trial utilizing the infiltration of a long-active multivesicular liposome formulation of bupivacaine, Exparel (IMPROVE): a phase IV health economic trial in adult patients undergoing ileostomy reversal. *J Pain Res* 2013;6:549. <https://doi.org/10.2147/JPR.S46467>
 16. Patel MA, Gadsden JC, Nedeljkovic SS, Bao X, Zeballos JL, Yu V, et al. Brachial plexus block with liposomal bupivacaine for shoulder surgery improves analgesia and reduces opioid consumption: results from a multicenter, randomized, double-blind, controlled trial. *Pain Med* 2020;21:387-400. <https://doi.org/10.1093/pm/pnz103>
 17. Portillo J, Kamar N, Melibary S, Quevedo E, Bergese S. Safety of liposome extended-release bupivacaine for postoperative pain control. *Front Pharmacol* 2014;5:9. <https://doi.org/10.3389/fphar.2014.00090>
 18. Riazi S, Carmichael N, Awad I, Holtby RM, McCartney CJ. Effect of local anaesthetic volume (20 vs 5 ml) on the efficacy and respiratory consequences of ultrasound-guided interscalene brachial plexus block. *Br J Anesth* 2008;101:549-56. <https://doi.org/10.1093/bja/aen229>
 19. Sabesan VJ, Shahriar R, Petersen-Fitts GR, Whaley JD, Bou-Akl T, Sweet M, et al. A prospective randomized controlled trial to identify the optimal postoperative pain management in shoulder arthroplasty: liposomal bupivacaine versus continuous interscalene catheter. *J Shoulder Elbow Surg* 2017;26:1810-7. <https://doi.org/10.1016/j.jse.2017.06.044>
 20. Segal DN, Wilson JM, Staley C, Michael KW. The 5-item modified frailty index is predictive of 30-day postoperative complications in patients undergoing kyphoplasty vertebral augmentation. *World Neurosurg* 2018;116:e225-31. <https://doi.org/10.1016/j.wneu.2018.04.172>
 21. Seltzer JL. Hoarseness and Horner's syndrome after interscalene brachial plexus block. *Anesth Analg* 1977;56:585-6.
 22. Sethi PM, Brameier DT, Mandava NK, Miller SR. Liposomal bupivacaine reduces opiate consumption after rotator cuff repair in a randomized controlled trial. *J Shoulder Elbow Surg* 2019;28:819-27. <https://doi.org/10.1016/j.jse.2019.01.008>
 23. Singelyn FJ, Lhotel L, Fabre B. Pain relief after arthroscopic shoulder surgery: a comparison of intraarticular analgesia, suprascapular nerve block, and interscalene brachial plexus block. *Anesth Analg* 2004;99:589-92. <https://doi.org/10.1213/01.ANE.0000125112.83117.49>
 24. Traven SA, McGurk KM, Reeves RA, Walton ZJ, Woolf SK, Slone HS. Modified frailty index predicts medical complications, length of stay, readmission, and mortality following total shoulder arthroplasty. *J Shoulder Elbow Surg* 2019;28:1854-60. <https://doi.org/10.1016/j.jse.2019.03.009>
 25. Urmey WF, Gloegler PJ. Pulmonary function changes during interscalene brachial plexus block: effects of decreasing local anesthetic injection volume. *Reg Anesth Pain Med* 1993;18:244-9.
 26. Urmey WF, McDonald M. Hemidiaphragmatic paresis during interscalene brachial plexus block: effects on pulmonary function and chest wall mechanics. *Anesth Analg* 1992;74:352-7.
 27. Vandepitte C, Kuroda M, Witvrouw R, Anne L, Bellemans J, Corten K, et al. Addition of liposome bupivacaine to bupivacaine HCl versus bupivacaine HCl alone for interscalene brachial plexus block in patients having major shoulder surgery. *Reg Anesth Pain Med* 2017;42:334-41. <https://doi.org/10.1097/AAP.0000000000000560>
 28. Viscusi ER. Liposomal drug delivery for postoperative pain management. *Reg Anesth* 2005;30:491-6. <https://doi.org/10.1016/j.rapm.2005.05.001>
 29. Voskuil T, Hageman M, Ring D. Higher Charlson Comorbidity Index scores are associated with readmission after orthopaedic surgery. *Clin Orthop Relat Res* 2014;472:1638-44. <https://doi.org/10.1007/s11999-013-3394-8>
 30. Vyas KS, Rajendran S, Morrison SD, Shakir A, Mardini S, Lemaine V, et al. Systematic review of liposomal bupivacaine (Exparel) for postoperative analgesia. *Plast Reconstr Surg* 2016;138:748e-56e. <https://doi.org/10.1097/PRS.0000000000002547>
 31. Weller WJ, Azzam MG, Smith RA, Azar FM, Throckmorton TW. Liposomal bupivacaine mixture has similar pain relief and significantly fewer complications at less cost compared to indwelling interscalene catheter in total shoulder arthroplasty. *J Arthroplasty* 2017;32:3557-62. <https://doi.org/10.1016/j.arth.2017.03.017>
 32. Wilson JM, Holzgrefe RE, Staley CA, Schenker ML, Meals CG. Use of a 5-item modified frailty index for risk stratification in patients undergoing surgical management of distal radius fractures. *J Hand Surg Am* 2018;43:701-9. <https://doi.org/10.1016/j.jhssa.2018.05.029>
 33. Winnie AP. Interscalene brachial plexus block. *Anesth Analg* 1970;49:455-66.