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The use of regional anaesthesia for surgical intervention has minimal effect on functional outcomes following fracture nonunion repair☆

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ABSTRACT

Purpose: The purpose of this study was to determine the effect of regional anaesthesia as compared to general anaesthesia on clinical, functional, and radiographic outcomes following long bone fracture nonunion repair.

Methods: 262 patients who underwent operative repair of a long bone fracture nonunion and had at least 12 months of post-operative follow up were included in this study. Functional outcomes were assessed prospectively using the Short Musculoskeletal Function Assessment (SMFA) and Visual Analog Scale (VAS) pain scores prior to nonunion repair and at routine intervals post-operatively. Patients were divided into two matched groups based upon the type of anaesthetic method used in surgery. The regional anaesthesia cohort was composed of all patients who received regional anaesthesia (spinal anaesthesia or peripheral nerve block) alone or in addition to general anaesthesia, while patients who received general anaesthesia alone made up the general anaesthesia cohort. Univariate and multivariate analyses were performed to examine the effect of anaesthesia type on functional outcome scores, post-operative pain, bony healing, and complication rate.

Results: The regional anaesthesia and general anaesthesia cohorts each consisted of 131 patients. Multiple linear regression demonstrated there to be no significant association between anaesthetic method and total SMFA scores at all post-operative time points. Additionally, anaesthetic method was not associated with post-operative VAS pain scores, time to union, or the rate of post-operative complications.

Conclusion: In this cohort, the use of regional anaesthesia during operative repair of long bone fracture nonunion was associated with no significant difference in functional outcome scores or pain levels at all post-operative time points. Furthermore, the use of regional anaesthesia had no effect on the rate of post-operative complications. Either type of anaesthetic appears to be safe and effective in performing these surgeries.

Introduction

Superior pain control during the immediate post-operative period has been associated with higher patient satisfaction, earlier return of motion, and shorter hospitalization in orthopaedic surgery patients [1,2]. Additionally, decreased pain following orthopaedic surgery may aid recovery, decrease dependence on narcotics, and allow for better patient participation in rehabilitation exercises at post-operative physical therapy [2].

Among the options to help mitigate post-operative pain is the use of regional anaesthesia. Both spinal anaesthesia and peripheral nerve blocks have been demonstrated to be superior to general anaesthesia at controlling pain during the peri-operative time-frame for a number of orthopaedic procedures [1,3–5]. Given the improved pain control profile, it is possible that the use of regional anaesthesia may have positive effects on functional outcomes secondary to improved early physical therapy. While previous studies have demonstrated superior outcomes and improved joint motion following regional anaesthesia in some acute fracture repair procedures, there have been no studies published to date examining the effect of anaesthesia type on patient outcomes following operative repair of fracture nonunion [6–8]. The purpose of this study is to determine the effect of regional anaesthesia (spinal or peripheral nerve block) as compared to general

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anaesthesia on short- and long-term functional, radiographic, and clinical outcomes in operatively managed long bone fracture nonunions.

Methods

Between September 2004 and March 2017, 415 patients underwent fracture nonunion repair with one of three trauma fellowship-trained orthopaedic surgeons at a single academic institution. All patients provided written informed consent to be followed prospectively in a trauma research registry.

Fracture nonunion was diagnosed in patients with no evidence of progression to union on three consecutive plain radiographs performed at least six weeks apart or, in the event of indeterminate radiographs, lack of bony healing on computed tomography (CT). The operating surgeon classified each fracture nonunion according to the system of Weber and Cech [9]. In all patients who underwent prior fracture surgery, laboratory examinations, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were collected to evaluate for possible underlying infection.

The anaesthesiologist, surgeon, and patients made the decision of anaesthetic method (regional vs. general) pre-operatively based upon factors such as patient age, comorbidities, and injury pattern using a shared decision making model. Spinal anaesthesia was performed using 3 mL of 0.5% isobaric bupivacaine and peripheral nerve blocks were performed using ultrasound-guided administration of 0.5% bupivacaine or 0.5% ropivacaine. General anaesthesia was induced using propofol and rocuronium with maintenance via desflurane or isoflurane in oxygen and nitrous oxide. Analgesia was achieved using fentanyl and morphine. With respect to the nonunion repair, external fixation or open debridement of the nonunion site was performed in all cases with removal of any pre-existing or failed hardware. The choice of fixation method and use of supplemental bone grafting was determined by the operating surgeon. Operative data was recorded. There were no differences with respect to post-operative management or surveillance protocols between patients who received regional as opposed to general anaesthesia.

Functional status was evaluated in all patients prior to nonunion repair and post-operatively at 3 months, 6 months, 12 months, and long-term follow-up using the Short Musculoskeletal Function Assessment (SMFA) and Visual Analog Scale (VAS) pain scores. Additional data collected included patient demographics, injury information, anaesthetic method, nonunion treatment, and post-operative complications. Bony union was determined by the attending surgeon based upon demonstration of three or four bridging cortices on plain radiograph or CT scan.

Patients were divided into two groups based upon the type of anaesthetic method used. All patients who received regional anaesthesia (spinal anaesthesia or peripheral nerve block) alone or in addition to general anaesthesia comprised the regional anaesthesia cohort. A one-to-one matched general anaesthesia comparison cohort was randomly selected from all available patients who received general anaesthesia alone. Statistical methods were then used to assess for differences between the two groups. Statistics were calculated using IBM SPSS version 23 (Armonk, NY: IBM Corporation), with significance set at $p < 0.05$ for all analyses. Univariate analysis was performed using independent samples t-tests for continuous variables and chi-squared analyses for categorical variables. Additionally, a secondary analysis was performed using multivariate linear regression to assess for the effect of anaesthetic method on post-operative SMFA scores and VAS pain scores after controlling for possible confounding variables. Covariates analyzed as part of this multivariate analysis included: anaesthetic method, age, sex, body mass index (BMI), Charlson comorbidity index (CCI), tobacco use, open vs. closed injury, mechanism of injury, nonunion classification, time to nonunion repair, and site of nonunion.

Results

Of the 415 patients who underwent operative repair of a lower extremity long bone fracture nonunion, 335 (80.7%) had a minimum of 12 months of post-operative follow-up with complete data and were eligible for inclusion in this study. Of the 80 patients excluded due to inadequate follow-up, 38 (47.5%) received regional anaesthesia and 42 (52.5%) received only general anaesthesia. Of the 335 patients eligible for inclusion in this study, 131 (39.1%) received regional anaesthesia and comprised the regional anaesthesia cohort. The remaining 204 (60.9%) patients received only general anaesthesia, and 131 patients were randomly selected from that group to produce the final 1:1 matched general anaesthesia cohort. The regional anaesthesia cohort consisted of 69 patients who received spinal anaesthesia, 3 patients who received a femoral nerve block, 3 patients who received a sciatic/popliteal nerve block, 2 patients who received both a femoral nerve block and spinal anaesthesia, 22 patients who received an interscalene block, 19 patients who received a supraclavicular block, 10 patients who received an infraclavicular block, and 3 patients who received an axillary block. Of those who received regional anaesthesia, there were 39 femoral nonunions, 38 tibial nonunions, 36 humeral nonunions, 8 forearm nonunions, and 10 clavicle nonunions. Of those who received general anaesthesia, there were 49 femoral nonunions, 41 tibial nonunions, 21 humeral nonunions, 10 forearm nonunions, and 10 clavicle nonunions. A breakdown of anaesthesia type based on nonunion site is provided in Table 1.

A comparison of demographic, injury, and nonunion data between both groups is summarized in Table 2. The two groups did not differ with respect to any demographic, injury, or nonunion data.

Bony healing, complications, pre- and post-operative pain scores, and pre- and post-operative functional outcome scores are provided in Table 3. Duration of follow-up was significantly longer in patients who received general anaesthesia (28.5 months vs. 20.7 months, $p = 0.001$). Of the 262 patients included, 257 (98.1%) achieved union at a mean of 6.5 months. Five patients went on to persistent nonunion, two (1.5%) of whom received regional

Table 1
Breakdown of anaesthetic type based on nonunion site.

Nonunion Site & Anaesthesia Type	Number of Cases
Femur (N = 88)	
General Anaesthesia	49 (55.7%)
Spinal Anaesthesia	34 (38.6%)
Femoral Nerve Block	3 (3.4%)
Spinal Anaesthesia & Femoral Nerve Block	2 (2.3%)
Tibia/Fibula (N = 79)	
General Anaesthesia	41 (51.9%)
Spinal Anaesthesia	35 (44.3%)
Sciatic/Popliteal Nerve Block	3 (3.8%)
Humerus (N = 57)	
General Anaesthesia	21 (36.8%)
Interscalene Block	12 (21.1%)
Supraclavicular Block	18 (31.6%)
Infraclavicular Block	5 (8.8%)
Axillary Block	1 (1.8%)
Radius/Ulna (N = 18)	
General Anaesthesia	10 (55.6%)
Supraclavicular Block	1 (5.6%)
Infraclavicular Block	5 (27.8%)
Axillary Block	2 (11.1%)
Clavicle (N = 20)	
General Anaesthesia	10 (50.0%)
Interscalene Block	10 (50.0%)

Table 2
Demographic, initial injury, and nonunion data for the regional anaesthesia and general anaesthesia cohorts.

	Regional Anaesthesia (N = 131)	General Anaesthesia (N = 131)	P Value
Age (years)	51.5 ± 17.2	49.4 ± 16.3	0.296
Sex			0.323
Male	70 (53.4%)	62 (47.3%)	
Female	61 (46.6%)	69 (52.7%)	
Body Mass Index	29.1 ± 5.6	29.3 ± 6.9	0.811
Charlson Comorbidity Index	0.7 ± 1.1	0.6 ± 1.1	0.426
Tobacco Use			0.160
Smoker	15 (11.5%)	23 (17.6%)	
Non-Smoker	116 (88.5%)	108 (82.4%)	
Original Injury			0.404
Open	19 (14.5%)	24 (18.3%)	
Closed	112 (85.5%)	107 (81.7%)	
Injury Mechanism			0.108
High Energy	59 (45.0%)	72 (55.0%)	
Low Energy	72 (55.0%)	59 (45.0%)	
Nonunion Site			0.247
Femur	39 (29.8%)	49 (37.4%)	
Tibia/Fibula	38 (29.0%)	41 (31.3%)	
Humerus	36 (27.5%)	21 (16.0%)	
Radius/Ulna	8 (6.1%)	10 (7.6%)	
Clavicle	10 (7.6%)	10 (7.6%)	
Nonunion Class			0.276
Atrophic	74 (58.3%)	80 (62.5%)	
Hypertrophic	33 (26.0%)	23 (18.0%)	
Oligotrophic	20 (15.7%)	25 (19.5%)	
Time to Nonunion Surgery (months)	14.7 ± 21.6	14.5 ± 15.8	0.934

Table 3
A comparison of outcomes data for both the regional and general anaesthesia cohorts. Asterisks indicate variables that were significantly different between the two groups ($p < 0.05$).

	Regional Anaesthesia (N = 131)	General Anaesthesia (N = 131)	P Value
Duration of Follow-Up (months)	20.7 ± 15.9	28.5 ± 19.9	0.001*
Total SMFA Score			
Baseline	33.6 ± 22.3	42.3 ± 23.6	0.003*
3 Months Post-Op	24.6 ± 19.1	32.4 ± 20.0	0.003*
6 Months Post-Op	19.5 ± 17.6	26.2 ± 18.3	0.007*
12 Months Post-Op	17.6 ± 18.7	23.0 ± 21.2	0.043*
Latest Follow-Up	16.8 ± 17.5	21.7 ± 20.8	0.049*
VAS Pain Score			
Baseline	5.4 ± 2.6	5.4 ± 2.7	0.971
3 Months Post-Op	2.6 ± 2.4	3.2 ± 2.8	0.118
6 Months Post-Op	2.7 ± 2.7	2.8 ± 2.7	0.804
12 Months Post-Op	2.4 ± 2.5	2.8 ± 2.5	0.195
Latest Follow-Up	2.3 ± 2.7	2.6 ± 2.7	0.414
Time to Union (months)	6.3 ± 3.7	6.6 ± 3.2	0.556
Complications	8 (6.1%)	8 (6.1%)	0.999
Hardware Failure	4 (3.1%)	1 (0.8%)	
Persistent Nonunion	2 (1.5%)	3 (2.3%)	
IC Abscess/Hematoma	1 (0.8%)	3 (2.3%)	
Surgical Site Infection	1 (0.8%)	1 (0.8%)	

anaesthesia and three (2.3%) of whom received general anaesthesia. One patient in the general anaesthesia cohort who did not achieve union elected to undergo below-knee amputation (BKA) due to persistent pain at the fracture site and two patients elected to live with the fracture nonunion. Both patients who received regional anaesthesia and did not achieve union elected to live with their fracture nonunion. There was no difference between the regional and general anaesthesia cohorts with respect to time to union. Additionally, post-operative complication rate did not differ between groups ($p = 0.999$), as 6.1% of patients who received regional anaesthesia and 6.1% of patients who received general anaesthesia experienced a post-operative complication requiring return to the operating room. No patient in either cohort experienced an adverse reaction to anaesthesia.

Concerning post-operative pain and functional outcome scores, there were no differences between groups with respect to mean VAS pain score at baseline or at any post-operative time point. Mean total SMFA score, however, was significantly lower in the regional anaesthesia cohort as compared to the general anaesthesia cohort at baseline and at all post-operative time points (Table 3).

Both groups improved significantly from baseline by 3 months post-operatively. Over this time period, mean VAS pain scores improved by 2.8 points in the regional anaesthesia cohort ($p < 0.0005$) and by 2.2 points in the general anaesthesia cohort ($p < 0.0005$). Additionally, the mean total SMFA score improved by 9.0 points from baseline to 3 months post-operatively in patients who received regional anaesthesia ($p = 0.001$) and by 9.9 points in patients who received general anaesthesia ($p < 0.0005$). While both groups improved significantly from baseline, the magnitude of improvement in VAS pain score ($p = 0.507$) and total SMFA score ($p = 0.943$) did not differ significantly between groups.

The results of multivariate analyses to investigate the effect of anaesthetic method on post-operative SMFA scores and VAS pain scores after controlling for possible confounding variables are provided in Table 4. Anaesthetic method was not associated with mean VAS pain score or total SMFA score at any post-operative time point. Other variables were identified as significant predictors of post-operative pain and functional outcome score at various time points and are listed in Table 4.

Discussion

To our knowledge, this is the first study examining the effect of anaesthetic method on clinical and functional outcomes following operative repair of fracture nonunion. In this cohort, anaesthetic method was not associated with differences in post-operative functional outcome scores, post-operative pain levels, time to union, or post-operative complication rate. It is important to note that, while a univariate analysis demonstrated significantly better functional outcome scores at all post-operative time points in patients who received regional anesthesia alone or in addition to general anesthesia, multivariate analyses identified no association between anaesthetic method and post-operative functional outcome scores. Therefore, the differences identified in the univariate analyses are likely secondary to differences in baseline functional status between groups, rather than a true effect of anaesthetic method.

The results of this study differ from those of previous studies comparing regional to general anaesthesia for acute fracture repair. For example, spinal anaesthesia has been associated with less pain and improved function in the early post-operative period in patients undergoing fixation of an acute ankle fracture [10]. In patients undergoing repair of a distal radius fracture, regional anaesthesia has been shown to be associated with improved pain levels and functional outcome scores through 6 months post-operatively, with improved range of motion seen through latest follow-up [7]. Additionally, while no effect was found on functional outcome scores in patients undergoing open reduction and internal fixation of a tibial plateau fracture, spinal anaesthesia has been associated with decreased pain levels in the early post-operative period [6]. Several of these studies identified the use of

Table 4
Association of anaesthetic method with VAS pain scores and total SMFA scores at all post-operative time points after controlling for confounding variables. Other significant predictors ($p < 0.05$) are indicated with asterisks.

	B	95% Confidence Interval	P Value
VAS Pain Score (3 months)			
Anaesthetic Method	0.534	−0.182 to 1.250	0.143
VAS Pain Score (6 months)			
Anaesthetic Method	−0.078	−0.848 to 0.693	0.843
Nonunion Site	0.345	0.005–0.685	0.047*
VAS Pain Score (12 months)			
Anaesthetic Method	0.216	−0.467 to 0.899	0.534
Nonunion Site	0.369	0.079–0.659	0.013*
Open vs. Closed Injury	1.106	0.140–2.072	0.025*
VAS Pain Score (Latest)			
Anaesthetic Method	0.162	−0.534 to 0.858	0.646
Nonunion Site	0.559	0.265–0.853	< 0.0005*
Age	0.029	0.005–0.053	0.016*
Total SMFA Score (3 months)			
Anaesthetic Method	4.348	−0.542 to 9.238	0.081
Nonunion Site	6.815	4.753–8.876	< 0.0005*
Age	0.217	0.052–0.382	0.010*
Tobacco Use	8.062	0.754–15.369	0.031*
Total SMFA Score (6 months)			
Anaesthetic Method	4.087	−0.484 to 8.658	0.079
Nonunion Site	4.751	2.731–6.771	<0.0005*
Age	0.195	0.037–0.352	0.016*
Sex	6.552	1.545–11.560	0.011*
Body Mass Index	0.505	0.129–0.880	0.009*
Total SMFA Score (12 months)			
Anaesthetic Method	3.468	−1.467 to 8.403	0.167
Nonunion Site	4.905	2.848–6.961	<0.0005*
Age	0.214	0.045–0.383	0.014*
Sex	5.402	0.182–10.623	0.043*
Tobacco Use	12.886	5.825–19.947	< 00005*
Total SMFA Score (Latest)			
Anaesthetic Method	4.129	−0.601 to 8.859	0.087
Nonunion Site	3.763	1.759–5.766	<0.0005*
Age	0.238	0.074–0.402	0.005*
Tobacco Use	8.026	1.061 – 14.990	0.024*

regional anaesthesia during acute fracture repair to be associated with an improvement in functional outcome, however, the results of this study suggest that the functional benefits of regional anaesthesia may not extend to fracture nonunion repair [7,10]. While the source of improved function secondary to the use of regional anaesthesia for acute fracture repair is unclear, one possible factor likely contributing to this functional difference is improved range of motion (ROM). Unfortunately, post-operative ROM data were not available for all patients in this cohort and were not included in this analysis. Furthermore, the format of this study would yield a convoluted and unclear ROM analysis given that all long bone fracture nonunions were included, regardless of location and affected bone. Different nonunion locations warrant ROM measurements for different joints, and numerous ROM sub-analyses would be required in this study. The effect of anaesthetic method on joint ROM following fracture nonunion repair is a limitation of this study and an area for future research.

While previous studies found regional anaesthesia to be associated with reduced pain following acute fracture repair, the lack of such findings in this cohort suggest that the chronic pain of a fracture nonunion may fundamentally differ from the pain associated with an acute fracture [6,7,10]. While acute pain is mediated entirely by nociceptor peripheral sensory neurons, there are numerous biologic changes that occur both peripherally and centrally in patients with chronic sources of pain [11,12]. First, peripheral sensitization is a process that causes hyperalgesia due to changes in nociceptor kinetics and signaling thresholds secondary to inflammatory response [12–14]. In addition to peripheral processes, central sensitization refers to an increase in spinal cord nerve nociceptive pathway excitability that occurs due to prolonged acute pain pathway activation, inflammation, or nerve damage [12,15]. Together, peripheral and central sensitization partially explain the biology of chronic pain, however, numerous other pathways are involved, and the process underlying chronic sources of pain is not yet fully understood [12]. One possible explanation for the variability in the effect of regional anaesthesia on post-operative pain following acute fracture repair as opposed to fracture nonunion repair relates to these sources of chronic pain. While regional anaesthesia effectively targets peripheral nerves and, thus, the portion of chronic pain that occurs due to peripheral sensitization, perhaps central sensitization contributes to the persistent pain experienced by patients following fracture nonunion repair.

There has been a recent focus on improving pain management and reducing post-operative opioid use in patients undergoing total knee arthroplasty (TKA) and other lower extremity orthopaedic procedures [16]. Multiple studies have suggested that the use of regional anaesthesia leads to reduced post-operative pain and, subsequently, less narcotic use following TKA [17,18]. Unfortunately, an analysis of immediate post-operative pain was not included in this study because the earliest time point at which patients were examined following surgery was 3 months post-operatively. It is possible that regional anaesthesia is associated with reduced pain in the first days-to-weeks following surgery, and future research is warranted to examine the effect of anaesthesia type on pain and narcotic use in the immediate post-operative period following nonunion repair.

The effect of anaesthetic method on the rate of complications following orthopaedic surgery procedures is unclear. For example, regional anaesthesia has been found to be associated with a lower rate of surgical site infections, cardiopulmonary complications, need for transfusion, and incidence of thromboembolic disease following total joint arthroplasty [8,19]. Neuraxial blockade also has been associated with reduced mortality following surgery both alone and when combined with general anaesthesia [20]. On the other hand, spinal anaesthesia has been associated with a similar or higher rate of peri-operative complications following hip fracture surgery [21,22]. In this cohort, neither anaesthetic method was associated with an increased rate of post-operative complications and, thus, both should always be considered in these cases.

It is important to note that multiple variables other than anaesthetic method were identified as significant predictors of post-operative SMFA scores and VAS pain scores in our multivariate linear regression analyses. However, given that the purpose of this study was to perform a focused analysis of the effect of anaesthetic method on clinical, radiographic, and functional outcomes following fracture nonunion repair surgery, the examination of these additional factors falls outside the scope of this manuscript. Future research is warranted to provide a more thorough description of other pre-operative and intra-operative variables that affect outcomes following fracture nonunion repair.

There are several limitations to this study. First, the study's retrospective cohort design is susceptible to selection bias. To minimize this risk, one-to-one matching was used to develop the regional and general anaesthesia cohorts, and multivariate linear regression analyses were used to further reduce the risk of uncontrolled confounding variables. The use of 1:1 matched cohorts comes at the expense of reduced study power, as 74 patients who received only general anaesthesia were excluded to allow for cohort matching. This reduction in study power is necessary, however, to best isolate the effect of anaesthetic method on patient outcomes. Another limitation is the fact that the choice of anaesthesia type was not randomized, presenting another opportunity for the introduction of a selection bias. Additionally, while only three surgeons performed the operations examined in this study, the different anesthesiologists and types of anaesthetic

agents used were not controlled for. Lastly, as mentioned previously, this study would be strengthened by an analysis of additional post-operative data, including adjacent joint range of motion and patient narcotic use. Unfortunately, these data were not available for all patients and were not included in this study.

In conclusion, the results of this study suggest that the use of regional anaesthesia alone or in addition to general anaesthesia during long bone fracture nonunion repair has minimal effect on post-operative functional outcomes, post-operative pain levels, and rate of post-operative complications. Thus, either type of anaesthetic appears to be safe and effective in performing these surgeries. The choice of anaesthetic method remains a multifactorial decision that should be decided by the orthopaedic surgeon and anesthesiologist based on the patient's injury, medical history, and pain tolerance. Both patients and physicians should understand that, regardless of anaesthetic chosen, similar functional recovery and diminution of pain will be seen by one year after treatment.

References

[1] Stein BE, Srikumaran U, Tan EW, Freehill MT, Wilckens JH. Lower-extremity peripheral nerve blocks in the perioperative pain management of orthopaedic patients: AAOS exhibit selection. J Bone Joint Surg Am 2012;94:e167, doi:http://dx.doi.org/10.2106/JBJS.K.01706.

[2] Chelly JE, Ben-David B, Williams BA, Kentor ML. Anesthesia and postoperative analgesia: outcomes following orthopedic surgery. Orthopedics 2003;26:s865–871.

[3] Bruce BG, Green A, Blaine TA, Wesner LV. Brachial plexus blocks for upper extremity orthopaedic surgery. J Am Acad Orthop Surg 2012;20:38–47, doi:http://dx.doi.org/10.5435/JAAOS-20-01-038.

[4] Srikumaran U, Stein BE, Tan EW, Freehill MT, Wilckens JH. Upper-extremity peripheral nerve blocks in the perioperative pain management of orthopaedic patients: AAOS exhibit selection. J Bone Joint Surg Am 2013;95(1-13):e197, doi:http://dx.doi.org/10.2106/JBJS.L.01745.

[5] Bernucci F, Carli F. Functional outcome after major orthopedic surgery: the role of regional anesthesia redefined. Curr Opin Anaesthesiol 2012;25:621–8, doi:http://dx.doi.org/10.1097/ACO.0b013e328357a3d5.

[6] Manoli A, Atchabahian A, Davidovitch RI, Egol KA. Spinal anesthesia improves early pain levels after surgical treatment of Tibial plateau fractures. J Orthop Trauma 2017;31:164–7, doi:http://dx.doi.org/10.1097/BOT.0000000000000773.

[7] Egol KA, Soojian MG, Walsh M, Katz J, Rosenberg AD, Paksima N. Regional anesthesia improves outcome after distal radius fracture fixation over general anesthesia. J Orthop Trauma 2012;26:545–9, doi:http://dx.doi.org/10.1097/BOT.0b013e318238becb.

[8] Hu S, Zhang Z-Y, Hua Y-Q, Li J, Cai Z-D. A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. J Bone Joint Surg Br 2009;91:935–42, doi:http://dx.doi.org/10.1302/0301-620X.91B7.21538.

[9] Weber BG, Čech O. Pseudarthrosis: pathophysiology, biomechanics, therapy, results. New York: Grune & Stratton; 1976.

[10] Jordan C, Davidovitch RI, Walsh M, Tejwani N, Rosenberg A, Egol KA. Spinal anesthesia mediates improved early function and pain relief following surgical repair of ankle fractures. J Bone Joint Surg Am 2010;92:368–74, doi:http://dx.doi.org/10.2106/JBJS.H.01852.

[11] Dubin AE, Patapoutian A. Nociceptors: the sensors of the pain pathway. J Clin Invest 2010;120:3760–72, doi:http://dx.doi.org/10.1172/JCI42843.

[12] Mifflin KA, Kerr BJ. The transition from acute to chronic pain: understanding how different biological systems interact. Can J Anaesth 2014;61:112–22, doi:http://dx.doi.org/10.1007/s12630-013-0087-4.

[13] Chuang HH, Prescott ED, Kong H, Shields S, Jordt SE, Basbaum AI, et al. Bradykinin and nerve growth factor release the capsaicin receptor from PtdIns(4,5)P2-mediated inhibition. Nature 2001;411:957–62, doi:http://dx.doi.org/10.1038/35082088.

[14] Cunha TM, Verri WA, Schivo IR, Napimoga MH, Parada CA, Poole S, et al. Crucial role of neutrophils in the development of mechanical inflammatory hypernociception. J Leukoc Biol 2008;83:824–32, doi:http://dx.doi.org/10.1189/jlb.0907654.

[15] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10:895–926, doi:http://dx.doi.org/10.1016/j.jpain.2009.06.012.

[16] Baratta JL, Gandhi K, Viscusi ER. Perioperative pain management for total knee arthroplasty. J Surg Orthop Adv 2014;23:22–36.

[17] Macfarlane AJR, Prasad GA, Chan VWS, Brull R. Does regional anesthesia improve outcome after total knee arthroplasty? Clin Orthop Relat Res 2009;467:2379–402, doi:http://dx.doi.org/10.1007/s11999-008-0666-9.

[18] Pope D, El-Othmani MM, Manning BT, Sepula M, Markwell SJ, et al. Impact of age, gender and anesthesia modality on post-operative pain in total knee arthroplasty patients. Iowa Orthop J 2015;35:92–8.

[19] Helwani MA, Avidan MS, Ben Abdallah A, Kaiser DJ, Clohisy JC, Hall BL, et al. Effects of regional versus general anesthesia on outcomes after total hip arthroplasty: a retrospective propensity-matched cohort study. J Bone Joint Surg Am 2015;97:186–93, doi:http://dx.doi.org/10.2106/JBJS.N.00612.

[20] Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000;321:1493.

[21] Rashid RH, Shah AA, Shakoor A, Noordin S. Hip fracture surgery: does type of anesthesia matter? Biomed Res Int 2013;2013:252356, doi:http://dx.doi.org/10.1155/2013/252356.

[22] Whiting PS, Molina CS, Greenberg SE, Thakore RV, Obremskey WT, Sethi MK. Regional anaesthesia for hip fracture surgery is associated with significantly more peri-operative complications compared with general anaesthesia. Int Orthop 2015;39:1321–7, doi:http://dx.doi.org/10.1007/s00264-015-2735-5.