UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
GENERAL MEDICINE

INFLAMMATORY RESPONSE IN TOTAL KNEE ARTHROPLASTY

DOCTORAL THESIS SUMMARY

PhD Supervisor:

PROFESSOR MD. CÎRSTOIU CĂTĂLIN, PhD

PhD-Student:

MD. SEREA (căs. BRATU) ANGELICA

2022

Abbreviations list

BMI - body mass index

CRP - C reactiv protein

GA - general anesthesia

IL - interleukin

iPACK - inter popliteal artery and posterior capsule of the knee infiltration

LRA - locoregional anesthesia

MCP-1 - monocyte chemotactic protein

MSOF - multiple system organ failure

NSAIDs - nonsteroidal antiinflammatory drug

PNB - peripheral nerve blocks

SIRS - systemic inflammatory response syndrome

TKA - otal knee arthroplasty

TNF alfa - tumor necrosis factor

VAS - visual analog scale

Table of Contents

I. Introduction 2

II. The general section 4

III. The special section 5

1.Working hypothesis and general objectives 5

2. The general research methodology 5

3. Quantifying the inflammatory response in total knee arthroplasty in patients with locoregional versus general anesthesia 6

3.1. Introduction 6

3.2. Material and method 6

3.2.1. Patients 6

3.2.2. Technique 7

3.2.3. Collection and processing of inflammatory samples 8

3.3. Results 8

3.4. Discussion 17

4. Correlations between the inflammatory response and acute pain and early recovery of the joint functionality in primary knee arthroplasty 21

4.1. Introduction 21

4.2. Material and method 21

4.3. Results 21

4.4. Discussion 25

5. Conclusions and personal contribution 27

IV. References 31

I. Introduction

Total knee arthroplasty is one of the most common surgeries in the orthopedic field, with an estimated number of over 700,000 knee replacements performed annually in the United States. Due to the increase in life expectancy and average age in the general population, the number of patients with severe arthritic lesions having an indication for joint replacement is increasing. Thus, in the short term, the incidence of total knee arthroplasty is expected to increase by about 14.7% in Europe and 7.9% in the United States each year, and to reach an estimated annual number of 3 million patients by 2030 [1-2].

The emergence of new, less and less invasive surgical techniques, the widespread implementation of fast track programmes and the innovative anesthesia and analgesia techniques have led to a significant decrease in the length of hospitalisation and to improved prognosis and recovery of such patients. In view of these aspects, the significant prevalence of this pathology in the general population, and the fact that total knee arthroplasty is known to be one of the orthopedic procedures that generate a significant algic stimulus, it appears imperative to develop a well-standardised protocol for the perioperative management of this type of patients. The purpose of this protocol would be to establish a direct causal relationship between current evidence and practice and improved perioperative prognosis, both in the short and long term [3].

The plethora of locoregional anesthetic techniques available has led to controversial debates on establishing an ideal anesthetic and analgesic regimen for total knee arthroplasty. Numerous studies have attempted to correlate the analgesic modalities and the anesthetic agent used with patient outcome and prognosis. Although the results of the studies are not consistent, the existing data appears to be in favour of the locoregional anesthesia in terms of magnitude of postoperative pain, incidence of complications, functional recovery and mortality rate [4].

The trauma induced by surgery produces a systemic reaction known as the acute phase response. The systemic inflammatory response consists of a chain of liver-mediated reactions that modulate over 100 genes; as a result, it stimulates the synthesis of the molecules called cytokines, which prevent bleeding, fight infection and stimulate wound healing. Many studies have shown that the magnitude and duration of the systemic

inflammatory response correlates directly with tissue injury and is a predictor of poor prognosis [5].

Since many studies certify that the magnitude of the triggered SIRS is a reliable predictor for the occurrence of postoperative complications, this thesis aims to investigate whether there is a direct causal relationship between the perioperative management of TKA patients, in terms of the analgesia and anesthesia techniques used, and the magnitude of the systemic and local inflammatory response syndrome that is triggered. Many studies certify that the magnitude of the triggered SIRS is a reliable predictor for the occurrence of postoperative complications [6].

Thus, a prospective single-center study was conducted that involved 40 patients proposed for unilateral total knee arthroplasty in the Orthopedics and Traumatology Clinic of the Bucharest University Emergency Hospital (SUUB) between May 2019 and March 2021. The recruited patients were divided into two groups according to the chosen anesthesia and analgesia technique, as follows:

- for the patients in the first batch, surgery was performed under general anesthesia and postoperative analgesia was administered using a multimodal intravenous analgesia protocol;
- for the patients in the second batch, surgery was performed under spinal anesthesia combined with continuous adductor canal block and iPACK, postoperative analgesia was administered with a multimodal analgesia protocol including, in addition to systemic analgesia, associated peripheral nerve blocks.

The main objective of the study was to quantify the differences in inflammatory response between the two batches. The inflammatory response was assessed by measuring the dynamics of the classical parameters of inflammation, namely the leukocyte count, fibrinogen and CRP, on the one hand, and the changes in the concentrations of some cytokines and chemokines, IL-6, IL-8 and MCP-1, on the other hand, which are considered to be more reliable in assessing the magnitude of the triggered inflammatory syndrome. The choice of biomarkers to be investigated was made based on the evidence in the literature to date, as well as by taking into account the availability of tests and the testing methodology required in order to conduct this study [7].

Considering that there are studies showing a local inflammatory response more than 100 times more intense than the systemic one, as well as the fact that the local inflammatory response could have a particular implication in the early recovery process of

the prosthetic joint, the above-mentioned inflammatory markers were monitored in parallel, both at systemic and local level [8].

The secondary objective of the study is to examine the causal relationship between the anesthetic and analgesic technique used and the postoperative pain and the early recovery of the joint functionality.

II. The general section

This first part of this doctoral thesis describes essential notions of surgical technique, anesthesia and analgesia in total knee replacement. The role played by the choice of anesthesia and analgesia techniques in determining prognosis and complications in total knee arthroplasty has been intensely discussed for a long time and is a controversial topic. Despite efforts and research, there is still no clear evidence to support the choice of optimal anesthetic and analgesic technique in terms of postoperative prognosis [9-10].

As the majority of patients proposed for total knee arthroplasty are generally compatible with any of the currently available anesthetic techniques, selecting the optimal technique for the surgical procedure is a challenge for the anesthetic practitioner[11-12].

The trauma induced by the surgical procedure entails a chain of metabolic and hemodynamic reactions, as well as significant changes in the immune response. Postoperative changes in the immune response are recognised as a series of reactions that ultimately aim to restore the body's balance and homeostasis in the postoperative period and consist in the release of inflammatory mediators, cytokines and acute phase reactants. The body's immune response is influenced by both the choice of anesthetic technique and the local anesthetic used [12-13].

Therefore this part of the paper also describes the inflammatory changes induced by the anesthetic-surgical procedure, the systemic and local consequences of a prolonged and sustained inflammatory response and the potential role of new techniques of ultrasound-guided locoregional anesthesia in limiting postoperative inflammation. [12][14-16]

In conclusion, the general part details the theoretical foundations underpinning the initiation of the study that is the subject of this doctoral thesis.

III. The special section

1.Working hypothesis and general objectives

Starting from the hypothesis that the exaggerated inflammatory response is a factor of unfavourable prognosis for TKA patients [17], the research carried out in the framework of this doctoral thesis aims, as a main objective, to prove that the inclusion of new techniques of ultrasonographically guided locoregional anesthesia in the perioperative care protocol of TKA patients brings an undeniable advantage, by directly limiting the inflammatory response occurring as a result of surgical trauma and all the related adverse reactions [18].

At the same time, by limiting the inflammatory response, the secondary objective of the study is to examine the causal relationship between the anesthetic and analgesic technique used and postoperative pain, the recovery of the joint functionality and a decreased length of hospitalisation.

2. The general research methodology

The study which makes the subject of this doctoral thesis is a prospective single-centre study, carried out on a group of 40 patients that were proposed for unilateral total knee arthroplasty in the Orthopedics and Traumatology Clinic of SUUB. The enrolment of patients was carried out after the Ethics Committee agreed to it and the patients gave their informed consent.

The patients included in the study were divided into two equal groups according to the chosen anesthesia and analgesia technique: the first batch received general anesthesia and multimodal systemic postoperative analgesia, while the second batch received spinal anesthesia combined with continuous adductor canal block and iPACK and postoperative analgesia combined regional analgesia techniques with systemically administered analgesics.

The magnitude of the inflammatory response was assessed by determining the dynamics of the concentration of inflammatory mediators, at the systemic level and at the local, joint level. Both common markers of inflammation, i.e. CRP, fibrinogen and the

leukocyte count, and more sensitive mediators with faster kinetics from the cytokine/chemokine category, i.e. IL-6, IL-8 and MCP-1, were selected for monitoring.

The statistical comparison of medians was performed using the Mann-Whitney-Wilcoxon test for independent samples: a comparison between patients receiving locoregional or general anesthesia.

3. Quantifying the inflammatory response in total knee arthroplasty in patients with locoregional versus general anesthesia

3.1. Introduction

Many studies have sought to identify the perfect choice of anesthesia and analgesia for total knee arthroplasty, especially since there is now clear evidence confirming the role of the anesthetic technique in the postoperative outcome and prognosis for patients [11][19-20].

The vast majority of studies investigate the inflammatory syndrome in neuraxial anesthesia compared to general anesthesia, while only few researchers have turned their attention to the inflammation associated with peripheral nerve blocks [10].

Based on the hypothesis that a sustained and prolonged inflammatory syndrome is associated with an unfavourable postoperative outcome, our study seeks to strengthen the role of new ultrasound-guided locoregional anesthesia techniques in the perioperative management protocol of total knee arthroplasty [21].

3.2. Material and method

3.2.1. Patients

The surgery was performed by specialist surgeons of the Orthopedics and Traumatology Clinic of SUUB through a medial parapatellar approach, and bicompartmental prostheses were implanted with component cementing. During the surgery hemostatic tape was used for all patients.

Patients were divided into two groups according to the anesthesia and analgesia technique that was used, as follows:

● the first batch: general balanced anesthesia with volatile pivot and multimodal postoperative analgesia, intravenous;

● the second batch: spinal anesthesia combined with continuous adductor canal block and infiltration between the popliteal artery and the posterior knee capsule (iPACK); postoperative analgesia was multimodal, combining regional anesthesia (continuous injection at the level of the adductor canal catheter) and intravenous analgesia.

3.2.2. Technique

The patients receiving general anesthesia were admitted directly to the operating room for anesthetic induction and surgery, while the patients receiving locoregional anesthesia were admitted to the preoperative ward for peripheral nerve blocks. Ultrasound-guided continuous adductor canal block was performed by injecting 20 ml ropivacaine 0.5% at the adductor canal and subsequently mounting a catheter (Contiplex Touhy Ultra Bbraun) in the medial portion of the canal, and iPACK was performed by ultrasound infiltration of 20 ml ropivacaine 0.5% (Stimuplex Ultra 360 20G-100 mm BBraun needle) in the space between the popliteal artery and the posterior knee capsule. Subsequently, spinal anesthesia with 15 mg bupivacaine 0.5% is performed in the operating room. Preoperatively, all patients received prophylactic antibiotic therapy with 2nd generation cephalosporins, which was continued in the postoperative course until drainage tubes were removed.

Intra-anesthetic monitoring was standard, patients were maintained normothermic and euvolemic by the administration of crystalloid solutions and blood products where necessary.

Immediately after surgery, all patients were admitted to the postoperative surveillance unit for vital functions monitoring and surveillance. The following parameters were monitored:

● the vital functions (TAM, AV, FR, SpO2);

● the volume of suction drainage from the prosthesis;

● VAS at rest and during mobilisation (from postoperative day 2);

● the degree of joint mobilisation (from postoperative day 2).

From postoperative day 2, patient mobilisation was started, first passively with the help of the Kinetec machine until the drain tubes were removed, later on also actively, by mobilisation to walk with support. The pain score (VAS) at rest and during mobilisation,

the degree of joint flexion and the potential less desirable events such as falling or muscle weakness were recorded. Patients were monitored in terms of clinical outcome until discharge from our unit.

3.2.3. Collection and processing of inflammatory samples

Venous blood samples were collected preoperatively and then at 24 and 48 hours postoperatively. Joint drainage fluid samples were collected immediately after surgery and then at 24 and 48 hours postoperatively. For the determination of cytokines and chemokines, blood was collected in special tubes with activating gel, subsequently centrifuged 10 min at a speed of 1400 rpm. The resulting serum was immediately transferred into 1.8 ml cryotubes, labelled with the patient's identification data, stored initially at -20 degrees Celsius, subsequently at -80 degrees Celsius, until processing. For IL-6, IL-8 and MCP-1, Elisa Elabscience kits were used with the following specifications:

- Elisa human IL6 kit with detection range 1.56-100 pg/ml, sensitivity 0.94 pg/ml;
- Elisa IL8 kit with detection range 7.81-500 pg/ml, sensitivity 4.69 pg/ml;
- Elisa MCP-1 kit with detection range 62.50-4000 pg/ml, sensitivity 37.50 pg/ml.

The testing method is based on the enzyme-linked immunosorbent assay technique (ELISA), more precisely its non-competitive variant called 'sandwich' ELISA. Results were expressed in pg/ml.

The CRP measurement was carried out by immunoturbidimetry and the results were expressed in mg/dl.

3.3. Results

From a demographical point of view there were no statistically significant differences between the two groups (Tabel III.1.)

Tabel III.1. Demographic characteristics

Demographic characteristics	Total N (%)	Locoregional anesthesia N (%)	General anesthesia N (%)	p value
Age (mean,y)	68.0 (59.0-71.0)	70.0 (62.0-72.0)	66.0 (59.0-70.7)	0.185
Sex woman man	 29 (72.5) 11 (27.5)	 14 (70.0) 6 (30.0)	 15 (75.0) 5 (25.0)	0.723
BMI (mean) kg/m2	31.9 (28.3-36.5)	32.5 (27.7-36.5)	31.5 (29.0-36.5)	0.645
VAS score admission (mean)	3.5 (3.0-4.0)	3.5 (3.0-4.0)	3.5 (3.0-4.0)	0.882
NSAID consumption	14 (35.0)	8 (40.0)	6 (30.0)	0.507
Opioids consumption	4 (10.0)	2 (10.0)	2 (10.0)	1.000
Comorbidities Cardiovascular disease Diabetes Cancer Cronic kidney disease Respiratory disease	 35 (87.5) 11 (27.5) 3 (7.5) 2 (5.0) 2 (5.0)	 17 (85.0) 7 (35.0) 0 (0.0) 1 (5.0) 0 (0.0)	 18 (90.0) 4 (20.0) 3 (15.0) 1 (5.0) 2 (10.0)	 0.633 0.288 0.072 1.000
Surgical time (mean, min)	147.5(100.0-150.0)	135.0 (100.0-150.0)	150.0 (130.0-157.5)	0.187
Transfusion No transfusion 1 U RBC 2 U RBC	 34 (85.0) 2 (5.0) 4 (10.0)	 17 (85.0) 2 (10.0) 1 (5.0)	 17 (85.0) 0 (0.0) 3 (15.0)	0.223

Analysis of inflammatory markers

The absolute leukocyte count changes significantly in the first 48 hours after surgery, peaking at 24 hours postoperatively (in our case 19,100/mmc), and then it follows a downward slope. The group with spinal anesthesia and PNB had a statistically significantly lower number of leukocytes at 24 hours postoperatively compared to the group with GA (median 11,200/mmc vs. 9,650/mmc Mann-Whitney U test = 90.00; p = 0.038) (Tabel III.2.). The one-way analysis of variance with correlated scores among the two groups of patients showed significant changes in leukocytes at the three points in time (F=7.81; p=0.008; partial η^2=0.167).

Tabel III.2. Leucocite count at 24 h relative to anesthesia type

24 hours postoperative (T1)			
	Locoregional anesthesia	General anesthesia	Total
Mean	9740,00	11435,00	10587,50
Median	9650,00	11200,00	10450,00
Standard deviation	3039,113	3094,184	3146,523
Minimum	3700	7400	3700
Maximum	19100	17600	19100
Test Mann-Whitney U=90,00; p value=0,038			

The analysis of the number of nucleated elements in the joint drainage fluid did not show statistically significant differences between the two groups. At the same time, the number of nucleated elements does not show any statistically significant variance over time between the times of examination.

Fibrinogen, another acute phase reactant analysed, shows statistically significantly higher values in the GA group compared to the spinal anesthesia and PNB group at 48 hours postoperatively (median 468.50 mg/dl vs. 345.37 mg/dl Mann-Whitney U test = 90.00; p = 0.038). At 24 hours postoperatively, although the plasma concentration of fibrinogen in the general anesthesia group was higher than in the spinal anesthesia and PNB group, the differences were statistically insignificant (median 345.00 mg/dl vs. 331.00 mg/dl) (Tabel III.3.). The one-way analysis of variance with correlated scores

among the two groups of patients showed significant change in fibrinogen at the three points in time (F=93.47; p<0.001; partial η^2=0.716).

Tabel III.3. Concentration of plasmatic relative to anesthesia type

24 h postoperative (T1)			
	Locoregional anesthesia	General anesthesia	Total
Mean	347,633500	482,4295	459,9485
Median	345,375000	468,5000	454,0000
Standard deviation	72,7975425	89,87286	79,72901
Minimum	225,7100	370,00	302,19
Maximum	467,0000	672,00	672,00
Test Mann-Whitney U=90,00; p value=0,038			

Starting from comparable preoperative values, the plasma concentration of CRP showed statistically significantly higher values in the GA group compared to the spinal anesthesia and PNB group both at 24 and 48 hours postoperatively. The one-way analysis of variance with correlated scores among the two groups of patients showed significant change in plasma CRP concentration at the three points in time (F=162.43; p<0.001; partial η^2=0.806), both overall and within each group (Tabel III.4.).

Tabel III.4. Concentration of plasmatic CRP relative to anesthesia type

24 h postoperative (T1)			
	Locoregional anesthesia	General anesthesia	Total
Mean	32,69	40,23	36,46
Median	26,00	39,31	31,52
Standard deviation	21,99	16,88	19,72
Minimum	13,00	8,61	8,61
Maximum	112,70	81,00	112,70
Test Mann-Whitney U=120,00; p value=0,030			

48 h postoperative (T2)			
	Locoregional anesthesia	General anesthesia	Total
Mean	72,69	103,41	88,05
Median	63,62	86,87	73,96
Standard deviation	30,58	40,19	38,53
Minimum	30,13	50,00	30,13
Maximum	141,00	206,90	206,90
Test Mann-Whitney U=95,00; p value=0,004			

CRP concentrations in joint drainage fluid however did not differ significantly between the two groups in the postoperative period, although the one-way analysis of variance with correlated scores among the two groups of patients showed significant change in the CRP concentration in joint aspiration fluid at the three points in time ($F=84.59$; $p<0.001$; partial $\eta^2=0.713$).

The plasma concentration of IL-6 was statistically significantly higher in the GA group compared to the spinal anesthesia and PNB group at 48 hours postoperatively (Tabel III.5.). The one-way analysis of variance with correlated scores among the two groups of patients showed significant change in plasma IL-6 concentration at the three points in time ($F=12.98$; $p<0.001$; partial $\eta^2=0.276$).

Tabel III.5. Concentration of plasmatic IL-6 relative to anesthesia type

48 h postoperative (T2)			
	Locoregional anesthesia	General anesthesia	Total
Mean	156,43	221,76	188,16
Median	43,03	124,92	51,67
Standard deviation	409,85	214,50	326,71
Minimum	18,83	27,01	18,83
Maximum	1777,67	811,91	1777,67
Test Mann-Whitney U=83,00; p value=0,020			

IL-6 concentration in joint drainage fluid showed statistically significantly higher values in the GA patient group immediately after surgery and at 48 hours postoperatively (Tabel III.6.). A one-way analysis of variance with correlated scores among the two groups of patients showed significantly different IL-6 concentration in the joint at the three points in time ($F=137.06$; $p<0.001$; partial $\eta^2=0.801$).

Tabel III.6. IL-6 concentration in drainage fluid relative to anesthesia type

Immediately postoperative (T0)			
	Locoregional anesthesia	General anesthesia	Total
Mean	843,56	2373,51	1586,68
Median	44,89	1371,00	156,72
Standard deviation	1560,81	2391,46	2123,98
Minimum	1,6	7,22	1,60
Maximum	4321,98	6377,24	6377,24
Test Mann-Whitney U=90,00; p value=0,038			
48 h postoperative (T2)			
	Locoregional anesthesia	General anesthesia	Total
Mean	5690,33	6122,69	5900,33
Median	5625,52	6377,24	5844,49
Standard deviation	356,16	340,97	407,68
Minimum	5094,36	5320,23	5094,36
Maximum	6377,24	6377,24	6377,24
Test Mann-Whitney U=54,50; p value=0,001			

As for IL-8, it does not provide significant information in the context of inflammation, as neither systemic nor joint concentration differed significantly between the two groups. The plasma concentration of IL-8 does not change significantly over the monitored period, suggesting that IL-8 synthesis would be triggered by stronger traumatic stimuli than in total knee arthroplasty. Joint IL-8 concentration shows statistically

significant changes at the three points in time analysed both overall and for each individual group (F=67.79; p<0.001; partial η^2=0.666).

The plasma concentration of MCP-1, similar to IL-6, had statistically significantly higher values in the GA group compared to the spinal anesthesia and PNB group at 48 hours postoperatively, while preoperative tests showed concentrations without significant differences between the two groups (Tabel III.7.). A one-way analysis of variance with correlated scores among the two groups of patients showed significant change in plasma MCP-1 concentration at the three points in time (F=7.89; p=0.001; partial η^2=0.188).

Tabel III.7. Concentration of plasmatic MCP-1 relative to anesthesia type

48 h postoperative (T2)			
	Locoregional anesthesia	General anesthesia	Total
Mean	532,50	629,36	579,55
Median	494,77	635,05	549,18
Standard deviation	180,08	179,31	183,73
Minimum	253,57	302,11	253,57
Maximum	919,03	953,28	953,28
Test Mann-Whitney U=88,00; p value=0,047			

At the joint level, MCP-1 concentration in drainage fluid shows statistically significantly higher values immediately after surgery for the general anesthesia group compared to the spinal anesthesia and PNB group. Subsequently, the differences between the two groups studied are statistically insignificant (Tabel III.8.). A one-way analysis of variance with correlated scores among the two groups of patients showed significant changes in MCP-1 concentration in the joint at the three points in time (F=190.21; p<0.001; partial η^2=0.848).

Tabel III.8. MCP-1 concentration in drainage fluid relative to anesthesia type

Immediately postoperative (T0)			
	Locoregional anesthesia	General anesthesia	Total
Mean	448,63	763,62	601,63
Median	500,23	694,51	554,75
Standard deviation	186,98	537,53	423,04
Minimum	145,60	246,54	145,60
Maximum	712,19	2628,86	2628,86
Test Mann-Whitney U=78,00; p value=0,013			

An analysis of the correlations between inflammatory marker concentrations at the three points in time reveals a close relationship between the initial magnitude of the inflammatory syndrome and its rise in the postoperative period. Thus, there will be a positive correlation between preoperative leukocyte count (Tabel III.9.) and fibrinogen concentrations (Tabel III.10.) and concentrations recorded at 24 and 48 hours postoperatively, respectively.

Tabel III.9. Correlations of leucocite count

		Leucocite count to T1 (nr./mm3)	Leucocite count to T2 (nr./mm3)
Leucocite count to T0 (nr./mm3)	rho	,502**	,513**
	p value	,001	,001
Leucocite count to T1 (nr./mm3)	rho	-	,618**
	p value	-.	,000

Tabel III.10. Correlations of plasmatic fibrinogen concentrations

		Plasmatic fibrinogen to T1 (mg/dl)	Plasmatic fibrinogen to T2 (mg/dl)
Plasmatic fibrinogen to T0 (mg/dl)	rho	,743**	,477**
	p value	,000	,002
Plasmatic fibrinogen to T1 (mg/dl)	rho	-	,654**
	p value	-.	,000

As regards the joint drainage fluid, there is a statistically significant positive correlation between the number of nucleated elements immediately after surgery (T0) and both the number of nucleated elements on postoperative day 1 (T1) and the number of nucleated elements on postoperative day 2 (T2) (Tabel III.11.).

Tabel III.11. Correlations of articulated nucleated cells

		Nucleated cells to T1 (nr./mm3)	Nucleated cells to T2 (nr./mm3)
Nucleated cells to To (nr./mm3)	rho	,392**	,411**
	p value	,018	,014
Nucleated cells to T1 (nr./mm3))	rho	-	,229
	p value	-.	,185

At the same time, there is a statistically significant positive correlation between preoperative plasma IL-6 concentration and 24-hour postoperative plasma IL-6 concentration, which in turn has a statistically significant positive correlation with 48-hour postoperative plasma IL-6 concentration (Tabel III.12.). At the joint level, there is a statistically significant positive correlation between IL-6 concentration in drainage fluid at 24 hours (T1) and the one at 48 hours (T2) (rho=0.385; p=0.022).

Tabel III.12. Correlations of IL-6 plasmatic concentrations

		Interleukin 6 to T1 (pg/ml)	Interleukina 6 to T2 (pg/ml)
Interleukin 6 to T0 (pg/ml)	rho	,420**	,317
	p value	,012	,063
Interleukin 6 to T0 (pg/ml)	rho	-	,772**
	p value	-.	,000

There is a statistically significant positive correlation between preoperative plasma IL-8 concentration and both 24- and 48-hour plasma IL-8 concentration (Tabel III.13.). At the joint level, there is a statistically significant positive correlation between IL-8 concentration in drainage fluid at 24 hours (T1) and the one at 48 hours (T2) (rho=0.791; p=0.000).

Tabel III.13 Correlations of IL-8 plasmatic concentrations

		Interleukin 8 to T1 (pg/ml)	Interleukin 8 to T2 (pg/ml)
Interleukin 8 to T0 (pg/ml)	rho	,392**	,411**
	p value	,018	,014
Interleukin 8 to T1 (pg/ml)	rho	-	,229
	p value	-.	,185

It should be noted that, at the intra-articular level, there is a statistically significant positive correlation between MCP-1 (rho=0.709; p<0.001) and CRP (rho=0.620; p<0.001) concentrations at 24 hours (T1) and the concentrations of the same inflammatory biomarkers at 48 hours (T2).

3.4. Discussion

Many studies have investigated the postoperative inflammatory response using serum cortisol, IL-6, the leukocyte count and the C-reactive protein as routine markers. It has also

been proven that there is a direct correlation between the extent of the triggered SRIS and the magnitude of injury produced in the surgical trauma of elective procedures. In this regard, in 2015, Watt and associates pooled the results of 164 studies involving 14,362 patients that underwent various surgical procedures and thus demonstrated the strong link between serum IL-6 and CRP levels and the extent of surgery. Further studies have sought to identify the inflammatory markers that most sensitively reflect the systemic inflammatory response induced in the postoperative course, as well as the various factors that may contribute to its initiation, amplification and maintenance, with subsequent progression to chronic inflammation and organ dysfunction [22].

Moreover, it has been proven that an exaggerated and prolonged inflammatory response will be associated with a higher incidence of postoperative complications such as lung and wound infections or digestive disorders [17].

In the study carried out in the Orthopedics and Traumatology Clinic of SUUB, perioperative monitoring of plasma IL-6 concentrations supports that locoregional anesthesia (spinal and PNB) is associated with a less intensive systemic inflammatory response compared to general anesthesia. Plasma IL-6 concentration shows statistically significantly higher values at 48 hours postoperatively in the group of patients that received general anesthesia and multimodal systemic postoperative analgesia. The CRP kinetics shows a similar evolution to that of IL-6. A comparative analysis of plasma CRP concentrations in the two groups shows statistically significantly higher values for patients with general anesthesia at 48 hours postoperatively. CRP correlates reliably with the extent of tissue injury in surgical trauma, which is also supported by the significantly greater increase in CRP in knee arthroplasty patients compared to hip arthroplasty patients [23].

Fibrinogen showed statistically significantly higher values at 48 hours postoperatively in patients that received general anesthesia and systemic multimodal analgesia compared to the spinal anesthesia and PNB group.

Another chemokine whose behaviour attracted the researchers' attention is interleukin 8, a cytokine with dual action, both pro- and anti-inflammatory. Among the enrolled patients, although the determined plasma IL-8 concentration shows higher values at 24 and 48 hours in patients with general anesthesia compared to patients with locoregional anesthesia, the differences do not meet the criteria for statistical significance. An analysis of the variability of plasma IL-8 concentrations over time shows statistically significant results only for the group of patients that received general anesthesia, while in the group of patients that received spinal anaesthesia and PNB the change in plasma IL-8

concentrations over time is insignificant. From a clinical point of view this may suggest the limiting effect of locoregional anesthesia on the systemic inflammatory response triggered by surgical trauma. However, we cannot support a conclusion on the usefulness of monitoring plasma IL-8 concentration for assessing the systemic inflammatory response induced by various types of anesthesia in total knee arthroplasty based on the available data from this study. Either the synthesis of this chemokine is likely to be triggered by traumatic stimuli much more aggressive than the anesthetic-surgical procedure in total knee arthroplasty or its monitoring should be performed at shorter intervals [7].

MCP-1, another inflammatory parameter that we chose to monitor in our study, is a widely studied chemokine whose utility has been gaining momentum recently. Its selection as one of the markers to assess the magnitude of inflammation post total knee arthroplasty was not accidental. There are currently numerous studies that show the involvement of MCP-1 in the transcription of physiopathological interactions underlying the development of many inflammatory pathologies such as lupus nephritis, hepatic fibrosis and the post-traumatic stress syndrome. [24-25]. This is why MCP-1 was included by a number of researchers on the list of the latest markers for assessing the extent of inflammation [26].

Starting from similar preoperative plasma values in the two groups, statistically significantly higher values are observed at 48 hours postoperatively in the general anesthesia group compared to the spinal anesthesia and PNB group. It appears that MCP-1 may be a novel biomarker for early diagnosis of aseptic decementation, its concentration being significantly increased in knee revisions compared to patients with osteoarthritis and primary prosthesis [27].

The leukocyte count, a parameter with a high degree of non-specificity, was also monitored in the patients included in the study. Although its value is certainly limited, it is a low-cost parameter and its availability is widespread. Preoperative CBC does not differ between the two groups of patients, but at 24 hours postoperatively, the leukocyte count is statistically significantly higher for patients in the general anesthesia group, but the difference decreases at 48 hours postoperatively. The assessment of leukocyte dynamics over time does not show significant changes at the three points in time for any of the two groups, therefore we cannot argue that the evolution of leukocyte count in the two groups of patients could indicate a more intense inflammatory response associated with one or the other type of anesthetic and analgesic management used.

Local changes in inflammatory markers appear to be more significant than plasma changes. However, data is currently limited due to the increasing use of postoperative joint

drainage, to technical collecting difficulties and the increased risk of joint superinfection through frequent handling of drainage tubes. This is why the vast majority of researchers have focused on studying the inflammatory response at the systemic level rather than at the local level, and among the acute phase reactants the most commonly investigated remains C-reactive protein [23].

There are studies showing more than 1000-fold increases in IL-6 and CRP levels in aspiration fluid from the operative wound compared to systemic levels of the same mediators [28].

In our study, local joint IL-6 and MCP-1 concentrations were found to be 50-100 times higher than plasma levels.

Monitoring IL-6 concentrations in intra-articular aspiration fluid reveals statistically significantly higher values in patients with general anesthesia compared to those with locoregional anesthesia, both immediately after surgery and at 48 hours postoperatively. Local CRP concentration did not show statistically significant differences between the two groups, which could lead to the conclusion that monitoring the magnitude of the local inflammatory response should be performed based on more sensitive markers of inflammation than CRP. Intra-articular MCP-1 and IL-8 concentrations were also found to be statistically significantly higher immediately after surgery in patients with general anesthesia. In this context, the assessment of the local inflammatory response seems to be more reliably judged on the basis of changes in the concentration of IL-6 or chemokines with faster kinetics such as IL-8 and MCP-1. The general picture of local postoperative inflammation should be consolidated by further studies, but with the monitoring of chemokines at shorter intervals during the first 24 hours after surgery, given that there are studies describing a peak value of MCP-1 and IL-8 at 4 hours, followed by a steep drop in their concentration at around 24 hours postoperatively. This also supports the evidence from the study carried out in our clinic, which shows significantly higher joint cytokine values immediately after surgery among patients that received general anesthesia [29].

Another parameter that was monitored in the joint aspiration fluid was the number of nucleated elements. However, it did not provide clinically meaningful information, most likely because of its non-specificity. As a result, monitoring the number of nucleated elements in the joint aspiration fluid does not seem to bring any benefit for monitoring the evolution of the local inflammatory response after total knee arthroplasty.

4. Correlations between the inflammatory response and acute pain and early recovery of the joint functionality in primary knee arthroplasty

4.1. Introduction

Acute or chronic pain is the most common symptom encountered by orthopedic surgeons and the most common cause of referral [30]. Knowledge of the physiopathological mechanisms involved in the genesis and persistence of post knee arthroplasty pain is the main way to intervene for its effective control and thus avoid complications that may result from poor pain management [31].

4.2. Material and method

The secondary objective of this doctoral thesis was to study the correlations between the magnitude of the local and systemic inflammatory response in primary knee arthroplasty and the intensity of postoperative pain and the early recovery of joint functionality. Records were made of the pain score at rest and during mobilisation and of the joint flexion angle during the first 48 hours after surgery. The purpose was to see how local and systemic markers of inflammation at different points in time correlate with postoperative pain intensity and the degree of early joint mobility.

4.3. Results

As expected, the VAS pain score recorded statistically significantly lower values at all points in time for the group of patients with spinal anesthesia and PNB. Thus, locoregional anesthesia is associated with better pain control in the postoperative period, both at rest and during mobilisation. Also, the joint flexion angle shows statistically significantly higher values for patients with spinal anesthesia and PNB compared to those in the GA group during the first 48 hours after surgery.

There is a statistically significant positive correlation between the VAS pain score at rest on postoperative day 1 and the plasma concentrations of C-reactive protein (rho=0.375; p=0.017) and IL-6 (rho=0.580; p<0.001) and the IL-6 concentration in the joint drainage fluid (rho=0.424; p=0.011). There is a statistically significant positive

correlation between the VAS pain score during mobilisation on postoperative day 1 and the plasma concentration of C-reactive protein (rho=0.464; p=0.003), IL-6 (rho=0.529; p=0.001), MCP-1 (rho=0.461; p=0.005) and fibrinogen (rho=0.348; p=0.032). There is also a statistically significant positive correlation between the VAS pain score during mobilisation on postoperative day 1 and the IL-6 concentration in the joint drainage fluid (rho=0.463; p=0.005). At the same time, there is a statistically significant negative correlation between the VAS score during mobilisation on postoperative day 1 and the IL-8 concentration in the joint drainage fluid (Tabel IV.1.).

Tabel IV.1. VAS - Inflammatory biomarkers correlations at 24 h postoperatively

Inflammatory biomarkers to T1		VAS at rest D1	VAS at mobilization D1
Plasmatic CRP	rho	,375*	,464**
	p value	,017	,003
Leucocite count	rho	-,034	,061
	p value	,835	,708
Fibrinogen	rho	,104	,348*
	p value	,533	,032
Plasmatic IL-6	rho	,580**	,529**
	p value	,000	,001
Plasmatic IL-8	rho	,176	,221
	p value	,311	,202
Plasmatic MCP-1	rho	,234	,461**
	p value	,176	,005
Articular IL-6	rho	,424*	,463**
	p value	,011	,005
Articular IL-8	rho	-,302	-,397*
	p value	,078	,018

There is a statistically significant positive correlation between the VAS score at rest on postoperative day 2 and the plasma concentrations of C-reactive protein, IL-6, IL-8, MCP-1 and fibrinogen, as well as with the IL-6 and CRP concentrations in joint drainage fluid. There is a statistically significant positive correlation between the VAS score during

mobilisation on postoperative day 2 and the plasma concentrations of C-reactive protein, IL-6, IL-8, MCP-1 and fibrinogen, as well as with the local CRP concentration at the joint level (Tabel IV.2.).

Tabel IV.2. VAS - Inflammatory biomarkers correlations at 48 h postoperatively

Inflammatory biomarkers to T2		VAS at rest D2	VAS at mobilization D2
Plasmatic CRP	rho	,604**	,659**
	p value	,000	,000
Leucocite count	rho	,244	,302
	p value	,130	,059
Fibrinogen	rho	,391*	,464**
	p value	,013	,003
Plasmatic IL-6	rho	,566**	,480**
	p value	,000	,003
Plasmatic IL-8	rho	,633**	,402*
	p value	,000	,017
Plasmatic MCP-1	rho	,554**	,565**
	p value	,001	,000
Articular CRP	rho	,513**	,398*
	p value	0,002	0,018
Articular IL-6	rho	,474**	,311
	p value	,004	,069
Articular IL-8	rho	-,132	-,179
	p value	,448	,304

There is a statistically significant negative correlation between the knee flexion angle on postoperative day 1 and the plasma concentrations of C-reactive protein and IL-6 (Tabel IV.3.).

Tabel IV.3. Knee flexion angle - Inflammatory biomarkers correlations at 24 h postoperatively

Inflammatory biomarkers to T1		Knee flexion angle D1
Plasmatic CRP	rho	-,373*
	p value	,018
Leucocite count	rho	-,154
	p value	,342
Fibrinogen	rho	-,117
	p value	,484
Plasmatic IL-6	rho	-,480**
	p value	,004
Plasmatic IL-8	rho	-,269
	p value	,118
Plasmatic MCP-1	rho	-,294
	p value	,086
Articular CRP	rho	-0,92
	p value	0,589
Articular IL-6	rho	-,328
	p value	,054
Articular IL-8	rho	,202
	p value	,244

There is a statistically significant negative correlation between the knee flexion angle on postoperative day 2 and the plasma concentrations of C-reactive protein, IL-6, IL-8 and MCP-1, as well as with the joint-level concentrations of CRP and IL-6. At the same time, there is a statistically significant positive correlation between the knee flexion angle on postoperative day 2 and the local IL-8 concentration (Tabel IV.4.).

Tabel IV.4. Knee flexion angle - Inflammatory biomarkers correlations at 48 h postoperatively

Inflammatory biomarkers to T2		Knee flexion angle D2
Plasmatic CRP	rho	-,577**
	p value	,000
Leucocite count	rho	-,262
	p value	,103
Fibrinogen	rho	-,228
	p value	,158
Plasmatic IL-6	rho	-,616**
	p value	,000
Plasmatic IL-8	rho	-,374*
	p value	,027
Plasmatic MCP-1	rho	-,578**
	p value	,000
Articular CRP	rho	-,388*
	p value	0,021
Articular IL-6	rho	-,513**
	p value	,002
Articular IL-8	rho	,377*
	p value	,025

Consequently, early joint mobility correlates directly with the degree of inflammation - the lower the degree of inflammation, the greater the knee flexion angle.

4.4. Discussion

In view of the evidence demonstrating that postoperative pain correlates directly with the magnitude of the systemic inflammatory response [32], it seems reasonable and warranted to focus efforts on studying the benefits that new locoregional anesthesia practices can bring to large-scale orthopedic surgery, as well as on investigating the correlations between pain intensity, joint mobility and cytokine concentration at the systemic and local level.

The anatomical studies performed on the corpses support the process of knowing the mechanism by which iPACK confers analgesia to the posterior territory of the knee joint. Therefore, following the recomandations of the literature, we used the technique of distal injection of local anesthetic, using a volume of 15 ml of ropivacaine 0.5%. None of the enrolled patients had damage to the motor branches of the sciatic nerve, clinically manifested by the impossibility of dorsiflexion of the forefoot [33] [35].

The recording of pain scores for the patients included in the study revealed a clear advantage for the patients in the group that received locoregional anesthesia and multimodal analgesia centered on the use of the continuous adductor canal block. Early joint recovery assessed on the basis of joint flexion angle was also superior in PNB patients, for whom a flexion angle of 60-70 degrees was recorded, which was statistically significantly higher than in patients with opioid-based analgesia, i.e. 45/55 degrees.

There is a statistically significant positive correlation between the pain score assessed according to the visual analogue scale and the plasma concentrations of IL-6 and CRP at 24 hours postoperatively, as well as with the plasma concentrations of CRP, IL-6, IL-8, MCP-1, leukocyte count and fibrinogen at 48 hours postoperatively. Statistically significant correlations were also found between the pain score and the CRP and IL-6 concentrations in intra-articular aspiration fluid. There is a statistically significant positive correlation between joint mobility and the plasma concentrations of inflammatory mediators of the acute phase protein and cytokine type (CRP, IL-6, IL-8, MCP-1) and the concentrations of CRP, IL-6 and IL-8 in the intra-articular aspiration fluid.

Demonstrating that peripheral nerve blocks can induce a blunted inflammatory response compared to general anesthesia and multimodal systemic analgesia is a small step forward in the management of this pathology. There is clearly a need for further studies on this subject, but the premises are encouraging.

Hall and associates studied the correlation between the inflammatory response and the functional recovery after total hip replacement and found that the magnitude of the inflammatory response correlates directly with postoperative pain and early functional recovery [20].

In another study by Feng and associates, this time on a cohort of total knee replacement patients, the same strong relationship was found between plasma IL-6 concentration and pain intensity at 48 hours postoperatively [34].

Urgas et al. proved that early postoperative recovery after total knee replacement is influenced by the local inflammatory response, but they did not find a direct causal relationship with IL-6 or CRP levels [8].

An interesting finding concerns the behaviour of IL-8 at the joint level. Based on the data of our study, it appears that IL-8 at the joint level has a predominantly anti-inflammatory activity. The intra-articular level of IL-8 correlates negatively with the pain score during mobilisation (the higher the IL-8 concentration, the lower the pain score). At the same time, there is a statistically significant positive correlation with the degree of early joint flexion (the higher the IL-8 concentration the greater the joint flexion angle). We believe that this should make the object of further research, as intra-articular IL-8 concentration may provide important information related to pain control and early postoperative mobilisation.

5. Conclusions and personal contribution

1. Locoregional anesthesia and multimodal postoperative analgesia combining innovative locoregional techniques (continuous adductor canal block and iPACK) with systemic analgesics in the perioperative management protocol of patients with total knee arthroplasty is associated with the triggering of a blunted postoperative systemic inflammatory response compared to general anesthesia.
2. The vast majority of researchers are focusing their efforts on investigating the systemic inflammatory response.
3. The local response is difficult to assess for several reasons: increasingly limited use of joint drainage tubes, technical collecting difficulties, as well as an increased risk of infection due to frequent handling.
4. Plasma concentrations of CRP, IL-6, MCP-1 and fibrinogen are statistically significantly higher at 48 hours postoperatively in the group of patients that received general anesthesia than in the group of patients that received spinal anesthesia and PNB.
5. Plasma IL-6 and plasma CRP concentrations show similar kinetics as a result of tissue trauma induced by the surgical procedure.
6. Although plasma IL-6 concentration more accurately reflects the intensity of the inflammatory response triggered, plasma CRP concentration is monitored more frequently due to the widespread availability of this inflammation marker.

7. Local CRP concentration does not show significant differences in the local inflammatory response depending on the anesthesia-analgesia technique that was used.
8. The immediate postoperative local inflammatory response assessed based on IL-6, IL-8 and MCP-1 concentrations in the intra-articular aspiration fluid is much more pronounced in the group of patients that received general anesthesia compared to the patients that received spinal anesthesia and PNB.
9. Also, the local inflammatory response at 48 hours based on the IL-6 concentration in the intra-articular aspiration fluid is more pronounced in the general anesthesia group.
10. The local inflammatory response appears earlier and precedes the systemic inflammatory response triggered by the trauma associated with surgery.
11. More frequent testing is needed during the first 24 hours after surgery in order to more accurately understand the role of the new markers in assessing inflammation in this type of surgery.
12. The monitoring of plasma IL-8 concentrations does not show significant differences between the two types of anesthesia used in the total knee arthroplasty protocol, therefore based on the plasma IL-8 concentration we cannot state that a more pronounced inflammatory response is associated with one or the other of the two techniques that were compared.
13. Previous studies did not find a correlation between plasma IL-8 concentration and surgical trauma, possibly because this cytokine is likely to react to traumatic stimuli more intense than the surgical procedure or because its kinetics was not captured due to the wider monitoring intervals in our study.
14. In any case, as regards IL-8, monitoring concentrations at the local level provides more accurate information compared to monitoring systemic concentrations.
15. Monitoring the absolute number of leukocytes in the blood, as well as the number of nucleated elements in the intra-articular aspiration fluid are parameters with extremely low specificity that do not provide reliable information for assessing the inflammatory response post total knee arthroplasty, but they have the great advantage of being likely to be widely used in centres where access to the determination of biological markers with higher sensitivity is limited.
16. Although leukocytes are a non-specific inflammatory marker of limited value, in the case of the patients included in the study a leukocyte peak was recorded at 24 hours, unaccompanied however by febrile elevation, possibly due to the inclusion of acetaminophen in the postoperative analgesia protocol.

17. As regards the influence of other associated factors, such as age, sex (male), pre-existing comorbidities, on the inflammatory response, this study cannot provide relevant data because of the small number of patients monitored. Pre-existing studies confirm that the assessment of plasma CRP concentration is more strongly influenced by such factors than other cytokines.

18. The occurrence of postoperative complications (infections, cardiovascular complications) may be a confusing factor in the interpretation of the postoperative inflammatory response.

19. Total knee replacement is accompanied by a pronounced inflammatory response. Explanations for this may arise from the use of hemostatic tape on the one hand and the major surgery on the long bones on the other.

20. The initial inflammatory status of each individual patient will influence the magnitude and duration of the inflammatory response triggered in the postoperative course.

21. Elevated values of preoperative inflammatory markers will be accompanied by a sustained postoperative systemic inflammatory response, which clinically reflects into an increased incidence of infectious complications, increased mortality and difficult postoperative recovery.

22. Monitoring the preoperative inflammatory status will allow the identification of patients at risk of a complicated postoperative course and the adaptation of the perioperative management protocol accordingly.

23. The normalisation of CRP about 2 weeks after surgery with the interruption of the chain between the inflammation and coagulation cascades, as well as early mobilisation justify prophylactic antithrombotic therapy offered during this period, until the 3 parameters composing the Virchow triad (inflammation, hypercoagulability, venous stasis) return to normal preoperative status.

24. The systemic anti-inflammatory effect of local anesthetic cannot be excluded from the chain of physiopathological mechanisms inducing the attenuation of postoperative inflammation by locoregional anesthesia.

25. Postoperative pain stimulus, both at rest and during mobilisation, was more effectively controlled by locoregional analgesia compared to the intravenous multimodal analgesia protocol.

26. Local and systemic inflammatory response correlates with pain and the functional recovery of the joint in the immediate postoperative period.

27. The pain score assessed according to the visual analogue scale correlates positively with the plasma concentrations of IL-6 and CRP at 24 hours postoperatively and with the plasma concentrations of CRP, IL-6, IL-8, MCP-1, leukocyte count and fibrinogen at 48 hours postoperatively.

28. Statistically significant positive correlations were found between the pain score and the CRP and IL-6 concentrations in the intra-articular aspiration fluid.

29. The local IL-6 and MCP-1 levels were found to be 50-100 times higher than their systemic concentration.

30. The local inflammatory response, i.e. CRP, IL-6 and IL-8 concentrations in the intra-articular aspiration fluid, correlate with early postoperative functional recovery.

31. There is also a statistically significant correlation between joint mobility and the plasma concentrations of acute phase protein and cytokine inflammatory mediators (CRP, IL-6, IL-8, MCP-1).

32. Local joint IL-8 appears to have a predominantly anti-inflammatory action as it correlates negatively with the VAS pain score during mobilisation (the higher the IL-8 concentration, the lower the pain score) and positively with the postoperative joint flexion angle (the higher the IL-8 concentration, the higher the flexion angle).

IV. References

1. Kurtz SM, Ong KL, Lau E, et al. International survey of primary and revision total knee replacement. Int Orthop. 2011;35:1783-1789.

2. Ethgen O, Bruyere O, Richy F, Dardennes C, Reginster JY. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. J Bone Joint Surg Am 2004; 86-A: 963-74

3. Sandra L. Kopp, MD, Jens Borglum, MD, PhD. Anesthesia and analgesia practice pathway options for total knee arthroplasty. Regional Anesthesia and Pain Medicine 2017; 42:683-697

4. Soffin EM, Memtsoudis SG. Anesthesia and analgesia for total knee arthroplasty. Minerva Anestesiol 2018;84:1406-12.

5. William K. Oelsner, BS, Stephen M. Engstrom, MD, Michael A. Benvenuti, BS; Characterizing the acute phase response in healthy patients following total joint arthroplasty: predictable and consistent. The journal of arthroplasty.2016; 1-6

6. Chen XX, Wang T, Li J, Kang H. Relationship between inflammatory response and estimated complication rate after total hip arthroplasty. Chin Med J 2016;129:2546-2551

7. Wasko MK, Bobecka-Wesolowska K, Tomasiuk R, et al. Measurement of the inflammatory response in the early postoperative period after hip and knee arthroplasty. Clin Chem Lab Med. 2015; 1055

8. Ugraş AA, Kural C, Kural A, Demirez F, Koldaş M, Cetinus E. Which is more important after total knee arthroplasty: Local inflammatory response or systemic inflammatory response?. Knee. 2011;18(2):113-116

9. Zhu DJ, Schwarzkopf R. Modern trends in total knee arthroplasty. Orthop Muscul Syst 2013; 2: 138.

10. Simons MJ, Amin NH, Scuderi GR. Acute wound complications after total knee arthroplasty: prevention and management. J Am Acad Orthop Surg 2017; 25: 547-55.

10. Memtsoudis SG, Sun X, Chiu YL, et al. Perioperative comparative effectiveness of anesthetic tehnique in orthopedic patients. Anesthesiology; (2103) :1046-1058

11. Pugely AJ, Martin CT, Gao Y, Mendoza-Lattes S, Callaghan JJ. Differences in short-term complication between spinal and general anesthesia for primary total knee arthroplasty. J Bone Joint Surg Am. 2013; 95:193-199

12. Kohl BA., Deutschman CS. The inflammatory response to surgery and trauma. Curr Opin Crit Care. 2006; 12(4):325-332
13. Stevenson GW., Hall SC., Rudnick S. et al. The effect of anesthetic agents on the human imune response. Anesthesiology. 1990; 72: 542-552
14. Lisowska B., Maslinski W., Maldyk P. Perioperative inflammatory response in patients with rheumatoid arthritis undergoing orthopaedic surgery. Arch Med Sci. 2008; (5): 248-254.
15. Wylde V, Beswick A, Bruce J, et al. Chronic pain after total knee arthroplasty. EFFORT Open Rev. 2018;3(8):461-470
16. Campiglia L, Consales G, De Gaudio AR. Pre-emptive analgesia for postoperative pain control:a review. Clin Drug Investig. 2010;30:15-26
17. Chen XX, Wang T, Li J, Kang H. Relationship between inflammatory response and estimated complication rate after total hip arthroplasty. Chin Med J 2016;129:2546-2551
18. Bratu A, Cursaru A, Comanelea A, Cîrstoiu C. The use of IPACK and the continuous adductor canal block in the perioperative management of total knee prosthesis. Journal of military medicine. 2021(2);238-43
19. Yuan, S.C., et al. Adductor Canal Block for Total Knee Arthroplasty: A Review of the Current Evidence. (2016) J Anesth Surg 3(2): 199-207
20. Perlas A, Chan VW, Beattie S. Anaesthesia technique and mortality after total hip or knee arthroplasty: a retrospective, propensity score-matched cohort study. Anesthesiology. 2016; 125:724-731
21. Lisowska B, Szymanska M, Nowacka E. Anesthesiology and the cytokine network. Postepy Hig Med Dosw, 2013; 67:761-769
22. Watt DG, Horgan PG, McMillan DC. Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. Surgery. 2015;157(2):362-380
23. Hall GM, Peerbhoy D, Shenkin A, Parker CJ. Salmon P. Relationship of the functional recovery after hip arthroplasty to neuroendocrine and inflammatory response. Br J Anaesth. 2001; 87:537-542
24. Lee YH, Song GG. Urinary MCP-1 as a biomarker for lupus nephritis: a meta-analysis. Z Rheumatol. 2017 May;76(4):357-363.
25. Dalgard C, Eidelman O, Jozwik C, Olsen CH, Srivastava M, Biswas R, Eudy Y, Rothwell SW, Mueller GP, Yuan P, Drevets WC, Manji HK, Vythlingam M, Charney DS, Neumeister A, Ursano RJ, Jacobowitz DM, Pollard HB, Bonne O. The MCP-4/MCP-1

ratio in plasma is a candidate circadian biomarker for chronic post-traumatic stress disorder. Transl Psychiatry. 2017 Feb 7;7(2):e1025.
26. Singh S, Anshita D, Ravichandiran V. MCP-1: Function, regulation, and involvement in disease. Int Immunopharmacol. 2021 Dec;101(Pt B):107598.
27. Dasa V, Kramer JM, Gaffen SL, Kirkwood KL, Mihalko WM. Is monocyte chemotactic protein 1 elevated in aseptic loosening of TKA? A pilot study. Clin Orthop Relat Res. 2012 Jul;470(7):1879-84.
28. Krohn CD, Reikeras O, Aasen AO. The cytokines IL-1beta and IL-1 receptor antagonist, IL-2 and IL-2 soluble receptor-alfa, IL-6 and IL-6 soluble receptor , TNF-alpha and TNF soluble receptor I, and IL-10 in drained and systemic blood after major orthopaedic surgery. Eur J Surg 1999;165:101-109
29. Strey CW, Marquez-Pinilla RM, Markiewski MM, et al. Early post-operative measurement of cytokine plasma levels combined with pre-operative bilirubin levels identify high-risk patients after liver resection. Int J Mol Med. 2011;27(3):447-454.
30. Bratu A, Cursaru A, Comanelea A, Şerban B, Cîrstoiu C. Multimodal analgesia in primary bone tumors. Romanian Journal of Orthopaedic Surgery and Traumatology. 2021;4(1): 30-37. . https://doi.org/10.2478/rojost-2021-0006
31. Grosu I, Lavand'homme P, Thienpont E. Pain after knee arthroplasty: an unresolved issue. Knee Surg Sports Traumatol Arthrosc. 2014 Aug;22(8):1744-58
32. Si Hb, Yang, TM, Zeng Y. et al. Correlations between inflammatory cytokines, muscle damage markers and acute postoperative pain following primary total knee arthroplasty. BMC Musculoskelet Disord 18, 265 (2017)
33. Tran J, Giron AL, Peng P, Chan V, et al. Evaluation of the iPACK block injectate spread: a cadaveric study. Reg Anesth Pain Med. 2019;44:689-694
34. Feng Y, Ju H, Yang B, An H. Effects of a selective cyclooxygenase-2 inhibitor on prospective inflammatory reaction and pain after total knee replacement. J Pain 2008; 9: 45-52
35. Thobhani S, Scalercio L, Elliot CE, et al. Novel regional techniques for total knee arthroplasty promote reduced hospital length of stay: an analysis of 106 patients. Ochsner J. 2017;17(3):233-238

Manuscripts

1. **Bratu A**, Cursaru A, Comanelea A, Cîrstoiu C. The use of IPACK and the continuous adductor canal block in the perioperative management of total knee prosthesis. Journal of military medicine. 2021(2);238-43. http://www.revistamedicinamilitara.ro/archive-2021-no-2-2021-vol-cxxiv-may/

2. **Bratu A**, Cursaru A, Comanelea A, Şerban B, Cîrstoiu C. Multimodal analgesia in primary bone tumors. Romanian Journal of Orthopaedic Surgery and Traumatology. 2021;4(1): 30-37. https://rojost.ro/category/2021/