Marek Janiak, MD, Diplomate of ESAIC, EDRA

Optimizing the analgesic effect of peripheral nerve blocks in the search for solutions to chosen shortcomings in regional anesthesia

Dissertation on Doctorate in Medical and Health Sciences in the discipline of Medical Sciences

Supervisor: dr hab. n. med. Janusz Trzebicki

Co-supervisor: dr n. med. Marcin Kołacz

I Department of Anesthesiology and Intensive Care,

Medical University of Warsaw

Head of Department: dr hab. n. med. Janusz Trzebicki

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I would like to dedicate this work to my precious wife and children, for their enduring patience and love.

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LIST OF PUBLICATIONS

The thesis is based on the following papers:

Kolacz Marcin, Mieszkowski Marcin, **Janiak Marek***, Zagorski Krzysztof, Byszewska Beata, Weryk-Dysko Malgorzata, Onichimowski Dariusz, Trzebicki Janusz. Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation A randomised trial. *European Journal of Anaesthesiology* 2020; 37(9): 773-789. **DOI:** https://doi.org/10.1097/EJA.0000000000001193

Impact Factor (2023) = 4.33, MEiN = 100 points (*corresponding author)

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Impact Factor (2023) = 4.964, MEiN = 140 points

Janiak Marek, Gorniewski Grzegorz, Kowalczyk Rafal, Wasilewski Piotr, Nowakowski Piotr, Trzebicki Janusz. Effect of intramuscular tramadol on the duration of clinically relevant sciatic nerve blockade in patients undergoing calcaneal fracture fixation. A randomized controlled trial. *Healthcare* 2023, 11, 498. **DOI:** https://doi.org/10.3390/healthcare11040498

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I. LIST OF ABBREVIATIONS

ASA – American Society of Anesthesiologists

ASRA – American Society of Regional Anesthesia and Pain Medicine

CONSORT – CONsolidated Standards Of Reporting Trials

COVID-19 – COrona Virus Disease 2019

ECG – ElectroCardioGram

ERAS – Early Recovery After Surgery

ESRA – European Society of Regional Anaesthesia and Pain Therapy

FTB – Femoral Triangle Block

IQR – InterQuartile Range

ITM – Intrathecal Morphine

LA/LMZ – Local Anesthetic/Lek Miejscowo Znieczulający

LAST – Local Anesthetic Systemic Toxicity

LIA – Local Infiltration Analgesia

NIBP/NBP – Non-Invasive Blood Pressure

NCA – Nurse Controlled Analgesia

NRS – Numerical Rating Scale

NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

PACU – Post Anesthesia Care Unit

PASC – ParaSartorial Compartment Blocks

PCA – Patient Controlled Analgesia

PROSPECT – PROcedure SPECific postoperative pain managemenT

QLB – Quadratus Lumborum Block

RA – Regional Anesthesia

RA-UK – Regional Anaesthesia group of United Kingdom

RCT – Randomized Controlled Trial

SD – Standard Deviation

SSFNB – Single Shot Femoral Nerve Block

TAP/TAPB – Transversus Abdominis Plane Block

TKA – Total Knee Arthroplasty

II. ABSTRACT

Regional anesthesia (RA) is currently seen as a technique of anesthesia that provides optimal postoperative analgesia. Its effectiveness and safety depend on the availability of adequately trained practitioners and the proper qualification of patients. RA is being implemented into the anesthetic practice in growing numbers of versatile surgical procedures, and its proven benefits over solitary general anesthesia have placed RA into postoperative standards of patient care. Respectable international and national anesthesia, as well as pain societies, are incorporating nerve blocks in their recommendations and guidelines as they become everyday tools for the practicing clinician.

The immense boom of regional anesthesia techniques is in part due to the introduction of ultrasound imaging into clinical practice which allows for the visualization of anatomical spaces, and nerves as well as aids in guidance of the needle trajectory and drug deposition. Ultrasound guidance has opened a vast array of novel or rediscovered regional blocks. In recent years, a new subset of ultrasound-guided RA techniques known as fascial plane blocks has evolved with the aim of injecting adequately large volumes of local anesthetics (LA) within fascial planes to block peripheral nerve branches found within the fascia or for the LA to spread along the body planes to reach paravertebral spaces. The increased number of possible nerve blocks and adjuvants in clinical practice allows for the personalization and optimization of anesthesia.

The effect of individual central or peripheral nerve blocks may limit a fast patient recovery to full activity and disrupt the course of convalescence, which goes against present perioperative recovery pathways. Such issues, in combination with the increasing complexity of RA techniques, lead to new challenges facing the anesthesia provider, including: introduction of motor-sparing peripheral nerve blocks, presence of rebound pain following the passage of the sensory block, optimal choice of the regional block technique, and safe use of RA in day-case surgery. To answer some of these debates, one must perform well designed randomized clinical trials to gain scientific ground before introducing changes to everyday clinical practice.

The common objective of this thesis was the search for the most optimal use of peripheral nerve blocks to overcome select shortcomings in three distinct surgical scenarios.

The samples for the studies were chosen among patients undergoing surgery with predicted severe postoperative pain. The common interventions were modifications of peripheral nerve blocks that were compared to other RA modalities and in one study to a placebo. To assess the efficacy and safety of the regional blocks, the measured outcomes were assessments of postoperative pain control such as perioperative opioid consumption, opioid-related side effects, pain levels assessed by standardized scores, and time to first analgesic request.

In the first published manuscript (VI.1), we reported a randomized trial conducted in two university-affiliated tertiary care hospitals on a total of 101 adult patients scheduled for cadaveric renal transplantation. Study participants were allocated to either receive a Quadratus Lumborum Block type 2 (QLB) posterior to the quadratus lumborum muscle or a Transversus Abdominis Plane Block (TAPB) as part of the standardized anesthesia and care pathway. The study's main goal was to assess whether a unilateral QLB would be superior in reducing postoperative cumulative 24-hour opioid consumption when compared with a unilateral TAPB as the potential sensory coverage of the QLB is wider and may include alleviation of visceral pain. The study showed a statistically significant reduction in fentanyl use in the postoperative period, but no clinically significant benefits in pain intensity scores, incidence of opioid side effects or patient satisfaction levels.

In the second publication (VI.2), a total of 52 patients undergoing primary total knee arthroplasty (TKA) under spinal anesthesia were randomized into two groups. In the first group, participants received an additional 100 micrograms of intrathecal morphine (ITM) as part of standard spinal anesthesia, whereas in the second group, directly following a spinal block, they received a single shot distal femoral triangle block of the femoral nerve (SSFNB). The study aimed to compare the analgesic effect of these interventions with a special focus on possible opioid-related side effects. Our trial demonstrated equipotent analgesia and pain scores of both interventions, but with a statistically higher incidence of opioid-related side effects in the ITM group such as pruritus, nausea, and 2 patients in the ITM group required administration of naloxone due to respiratory depression, thus making ITM a suboptimal choice for day-case TKA.

In the third published randomized controlled trial (VI.3), we focused on intramuscular tramadol as an adjuvant for popliteal sciatic nerve block in patients undergoing pain-generating intramedullary calcaneal fracture fixation. The primary hypothesis was, that a 100

milligram of tramadol administered intramuscularly at the time of a popliteal block would extend the analgesic effect at least by 1.5 times covering night hours and protecting against severe rebound pain. The study results did not show a clinically meaningful sensory block extension or an opioid-sparing effect of tramadol for calcaneal fracture fixation.

In summary, the choice of the most suitable and optimal RA technique is still debated and requires further research. The three papers included in this dissertation help broaden our knowledge of the potential possibilities and effects of using different RA techniques in the chosen surgical procedures.

III. STRESZCZENIE

Optymalizacja wykorzystania obwodowych blokad nerwowych w poszukiwaniu rozwiązań wybranych ograniczeń regionalnej anestezji

Regionalna anestezja (RA) jest obecnie postrzegana jako technika znieczulenia pozwalająca zapewnić optymalną analgezję pooperacyjną. Jednak jej skuteczność i bezpieczeństwo jest uzależnione od odpowiedniego wyszkolenia lekarzy i prawidłowej kwalifikacji pacjentów. RA jest wykorzystywana do znieczulenia w coraz większej liczbie różnych zabiegów operacyjnych. Udowodnione korzyści RA, w porównaniu ze stosowaniem jedynie znieczulenia ogólnego, przyczyniły się do jej uznania jako standardu opieki pooperacyjnej. Renomowane towarzystwa anestezjologiczne oraz te, zajmujące się leczeniem bólu, uwzględniły blokady nerwów w swoich zaleceniach i wytycznych, co spowodowało, że RA jest wykorzystywana w codziennej praktyce klinicznej.

Intensywny rozwój technik RA wynika częściowo z wprowadzenia do praktyki klinicznej obrazowania ultrasonograficznego, czyli możliwości wizualizacji poszczególnych przestrzeni anatomicznych, nerwów, śledzenia trajektorii wprowadzanej igły i określenia docelowego miejsca dla deponowanego leku. Pozwoliło to na opracowanie szerokiego wachlarza nowatorskich lub odkrytych na nowo blokad regionalnych. W ostatnich latach powstała nowa podgrupa technik RA wykonywanych pod kontrolą ultrasonografii, które określono jako blokady powięziowe. Ich zadaniem jest blokada nerwów obwodowych poprzez podanie odpowiednio dużych objętości leku miejscowo znieczulającego (LMZ) do przestrzeni powięziowych lub rozprzestrzenianie się LMZ do przestrzeni przykręgowej. Zwiększona różnorodność blokad regionalnych oraz stosowanych adiuwantów w praktyce klinicznej pozwoliło na personalizację i optymalizację znieczulenia.

Wpływ poszczególnych blokad centralnych lub obwodowych może ograniczać szybki powrót pacjenta do pełnej aktywności i zaburzać przebieg jego rekonwalescencji. Jest to niezgodne z obecnymi zaleceniami postępowania okołooperacyjnego. Takie problemy jak i rosnąca złożoność technik RA prowadzą do pojawienia się nowych wyzwań dla anestezjologów. Należą do nich m.in.: wdrożenie blokad obwodowych oszczędzających motorykę, występowanie zjawiska bólu z odbicia po ustąpieniu blokady czuciowej oraz wybór

optymalnej techniki blokady regionalnej, a także poprawa bezpieczeństwa prowadzenia RA w chirurgii jednego dnia. Powyższe zagadnienia wymagają przeprowadzenia odpowiednio zaprojektowanych klinicznych badań randomizowanych, co może pozwolić na uzyskanie podstaw naukowych w celu wdrożenia ukierunkowanych zmian w codziennej praktyce klinicznej.

Wspólnym celem pracy doktorskiej było poszukiwanie optymalnego zastosowania różnych technik RA w wybranych zabiegach chirurgicznych. Do badań zakwalifikowano pacjentów poddanych zabiegom z przewidywanym silnym bólem pooperacyjnym. Wspólną interwencją była modyfikacja obwodowych blokad nerwowych, którą porównywano z innymi technikami RA, a w przypadku jednego badania do placebo. W celu określenia skuteczności i bezpieczeństwa badanych blokad regionalnych jako punkty końcowe poszczególnych badań przyjęto okołooperacyjne zużycie opioidów, działania niepożądane opioidów, natężenie bólu oceniane za pomocą standardowych skal oraz czas do pierwszego podania leku przeciwbólowego.

W pierwszej opublikowanej pracy (VI.1) przeprowadzono badanie randomizowane w dwóch ośrodkach klinicznych u 101 dorosłych pacjentów poddanych przeszczepieniu nerki od dawcy zmarłego. Zostali oni przydzieleni do dwóch grup. W jednej wykonano blokadę na tylnej powierzchni mięśnia czworobocznego lędźwi (Quadratus Lumborum Block QLB typu 2), a w drugiej blokadę w obrębie powięzi mięśnia poprzecznego brzucha (Transversus Abdominis Plane Block TAPB). Znieczulenie ogólne i opiekę pooperacyjną prowadzono jednakowo w obu grupach. Głównym celem badania była ocena, czy jednostronna blokada QLB może istotnie ograniczyć sumaryczne zapotrzebowanie na opioidy w pierwszych 24 godzinach pooperacyjnych w porównaniu z blokadą TAPB, ponieważ QLB ma potencjał do szerszego zakresu blokady czuciowej i może obejmować swoim zakresem ból trzewny. W badaniu wykazano statystycznie istotne zmniejszenie zapotrzebowania na fentanyl w okresie pooperacyjnym, ale bez klinicznie istotnych korzyści w zakresie zmniejszenia intensywności bólu ocenianego w odpowiednich skalach, częstości działań niepożądanych opioidów oraz poziomu satysfakcji pacjentów.

W drugiej pracy (VI.2) przedstawiono badanie obejmujące 52 pacjentów poddanych protezoplastyce całkowitej stawu kolanowego (TKA) w znieczuleniu podpajęczynówkowym.

Badani zostali randomizowani do dwóch grup. W pierwszej podawano dodatkowo do przestrzeni podpajęczynówkowej 100 mikrogramów morfiny (ITM - Intrathecal Morphine) podczas standardowego znieczulenia podpajęczynówkowego. Natomiast w drugiej, zaraz po znieczuleniu podpajęczynówkowym, wykonywano blokadę w dystalnej części trójkąta udowego w pojedynczym podaniu (SSFNB - Single Shot Femoral Nerve Branches Block). Celem badania było porównanie efektu analgetycznego powyższych interwencji, ze szczególnym uwzględnieniem możliwych działań niepożądanych opioidów. Badanie wykazało porównywalną analgezję w obu grupach, jednak z istotnie częstszym występowaniem działań niepożądanych opioidów w grupie ITM, takich jak świąd i nudności. W 2 przypadkach w grupie ITM wystąpiła niewydolność oddechowa, która wymagała podaży naloksonu. Powyższe wyniki wskazują, że wybór ITM może być suboptymalny w przypadku chirurgii jednego dnia.

W trzecim randomizowanym badaniu (VI.3) podawano tramadol domięśniowo jako adiuwant w blokadzie nerwu kulszowego w dole podkolanowym u pacjentów poddawanych zespoleniu śródszpikowym złamania kości piętowej. Główna hipoteza badawcza zakładała, że podanie domięśniowe 100 miligramów tramadolu jednoczasowo z wykonywaną blokadą nerwu kulszowego może wydłużyć okres analgetyczny co najmniej 1,5-krotnie, zapewniając bezbolesną noc i chroniąc przed bólem z odbicia. Wyniki badania nie wykazały klinicznie znaczącego przedłużenia blokady czuciowej ani zmniejszenia zapotrzebowania na opioidy w leczeniu bólu pooperacyjnego po zespoleniu kości piętowej.

Podsumowując, wybór odpowiednich i optymalnych technik RA nadal pozostaje dyskusyjny i wymaga dalszych badań. Powyższy cykl trzech prac naukowych, stanowiący dysertację doktorską, pozwala na poszerzenie naszej wiedzy w zakresie możliwości i skutków wykorzystania różnych technik RA w znieczuleniach do wybranych rodzajów operacji.

IV. INTRODUCTION

One of the core roles of anesthesia is to provide sufficient perioperative pain control to allow for the surgical procedure to be undertaken and to prevent unnecessary suffering of the patient in the postoperative period. These objectives are achieved by altering the perception of pain by the patient with general anesthesia, potent analgesics and blocking the sensation from parts of the body with regional anesthesia.

Regional anesthesia (RA) techniques are commonly divided into: central and peripheral nerve blocks. Administration of local anesthetic agents with or without adjuvants into the spinal canal leading to a typical bilateral and extensive anesthetic or analgesic effect describes a central or neuraxial block. On the other hand, a peripheral nerve block is an injection and spread of local anesthetic agents in proximity to nerve structures outside the spinal canal. A new subset of ultrasound-guided RA techniques, commonly called fascial plane blocks, has evolved in recent years: an injection of larger volumes of more dilute local anesthetic agents within fascial planes may anesthetize more extensive areas of the body and reach the deeper or distant peripheral and central nerve compartments with the benefit of less motor blockade [1,2]. Standard neurostimulator and anatomical-based RA techniques are also changing to more selective end-nerve blocks, quite often not visible even under ultrasound, but with a known anatomical location, such as a saphenous nerve block in the adductor canal. These newer blocks still have to find their place in patient care and perioperative pathways.

The unique analgesic effect of RA techniques and the exponentially growing choice of options for blocking nerves has shifted the focus on identifying the most optimal method for a given surgical procedure and on extending excellent analgesia into the postoperative period. A prolonged duration of regional anesthetic agents can be achieved by using continuous techniques via a catheter placed close to nerve structures, by combining adjuvant drugs with the injected local anesthetics such as steroids and opioids, or by modifying the local anesthetic into longer-release formulations in liposome or microsome structures. A yet-to-be-implemented direction may be peripheral nerve neuromodulation techniques with programmable stimulating catheters, thus avoiding the dangers of local anesthetic agents in ambulatory settings [3].

Due to the multitude of RA techniques, the introduction of modern anesthesia adjuncts, opioid-free anesthesia, minimally invasive surgical techniques, ambulatory surgery and enhanced recovery after surgery (ERAS) programs, the search for the most optimal nerve blocks for specific surgical scenarios is still under investigation. A lower number of research trials can be seen in more niche fields of surgery.

Taking into consideration the aforementioned aspects, research in RA modalities remains an interesting direction for the benefit of the patient, practitioner and health system. The scientific focus of the presented academic thesis was the optimization of ultrasound-guided RA techniques in three distinct clinical situations: kidney transplantation surgery, total knee arthroplasty and calcaneal fracture surgery.

IV.1 Short historical perspective: how we got here?

Carl Koller is still considered the father of modern RA, as he was the recognized discoverer of the use of cocaine for ophthalmological surgery in 1884. First descriptions of RA techniques rapidly followed: a direct brachial plexus blockade by William Halsted in 1884, spinal anesthesia by August Bier in 1898, and a percutaneous axillary brachial plexus by Georg Hirschel in 1911 [4]. A comprehensive textbook of RA was published in 1922 by Gaston Labat, and in combination with the discovery of safer local anesthetics such as procaine, led to widespread implementation of RA, in part due to the suboptimal and high-risk general anesthesia practice of the early 1900s [5].

However, in the middle of the 20th century, parallel improvements in general anesthesia and reports of serious complications due to RA including the Woolley and Roe cases of paraplegia following neuraxial anesthesia resulted in reduced interest in the practice of regional blocks, leaving it to enthusiasts [4,6].

It was not until the 1980s that renewed interest in RA gained momentum, with an enormous leap that is still occurring thanks in part to the development of ultrasound guidance and the incorporation of various regional blocks in multimodal analgesia and patient care pathways. In modern anesthesiology, RA techniques have become refined and supplementary to general anesthesia and sedation. Fascial plane blocks have found their place as potentially safe alternatives to epidural or paravertebral blocks. As an example, the transversus abdominis plane block (TAP) was the first to be adopted as an ultrasound-guided fascial plane block for

abdominal surgery, but many variations have occurred with a subcostal TAP, posterior TAP, and a further evolution called the quadratus lumborum block (QLB) group, targeting the spinal nerve closer to the intervertebral foramen, with a potential spread towards the paravertebral space [7,8,9].

IV.2 Benefits of regional anesthetic blocks: why should we want to invest in RA?

RA confers several benefits over solitary general anesthesia which include excellent acute pain control, prevention of chronic pain in certain surgical settings, reduced risk of postoperative nausea and vomiting, avoidance of airway interventions and secondary pulmonary complications. A connection of RA techniques with the reduction of cancer recurrence, blood transfusion requirements, surgical site infections and even mortality is considered [10,11]. Although several of these benefits lack strong evidence, there is an increased interest in RA during the last decade. This is partly a result of the introduction of ultrasound guidance for most RA techniques turning the practice into a skill for a larger community of practitioners rather than an art for a select few. With multiple new or rediscovered regional blocks under ultrasound guidance, the indications and benefits of such techniques have evolved greatly and are also under constant research [3,12,13].

The primary short-term benefit of a successful RA block in the postoperative period is its exceptional analgesic effect. With this effect, comes improved quality of recovery, earlier discharge from monitored care, and a decrease in opioid requirements following painful surgical procedures. Peripheral nerve blocks are becoming integrated into multimodal postoperative pathways [14].

The blockade of the surgical field reduces the stress responses, which together with a lower dosage of opioids, may reduce the recurrence of cancer. Although this has yet to be proven, the risk related to implementing the RA blocks would not outweigh the benefit of stopping cancer recurrence [15,16].

New evidence is emerging of RA blockades reducing the incidence of persistent postoperative pain syndromes in select patient groups. The possible mechanisms protecting the patient from developing chronic postoperative pain may include: the anti-inflammatory effect of local anesthetics, reduced sensitization of spinal and supraspinal pain centers and avoidance of inadequate pain control in the early postoperative period [17,18].

The role of RA is especially visible in demanding times such as the pandemic outbreak of COVID-19. The ASRA and ESRA societies have recommended shifting anesthesia from the general to more regional techniques avoiding airway manipulations and decreasing the insult to the respiratory system [19,20,21].

IV.3 Select shortcomings of regional anesthetic blocks and ways of overcoming them: what do we still need to work on?

Although the benefits of RA are multiple and directly impact the clinical outcomes of patients, the implementation of these techniques is still low [22,23]. One of the reasons is the definite lack of skilled anesthesiologists in many parts of the world [24,25]. Certain techniques require special equipment, such as the ultrasound machine with a dedicated transducer, specialist block needles, nerve stimulators constructed for peripheral nerve blocks, infusion devices for the local anesthetic, lipid emulsion rescue kits, and other safety drugs and equipment. In the last few years, the emergence of a multitude of fascial plane blocks and approaches to older blocks has left many clinicians confused [26,27]. It may be feasible to choose a less effective, but easy to implement regional block. The educational and practical gap among anesthesia providers is one of the future aims of advancing regional anesthesia. As an example, the Regional Anesthesia group of United Kingdom (RA-UK) has introduced the concept to teach seven basic blocks as part of Plan A blocks [12,28]. The choice of the block depends on new emerging evidence of clinical relevance and value, but also on the ease of performing the block and the safety profile. In this spirit, we performed a study to find the more optimal fascial plane block for renal transplantation to help resolve in part the choice dilemma (see the manuscript in section VI.1) It should be noted that neuraxial block techniques and deep peripheral nerve blocks require a normal coagulation status due to the risk of peri-neuraxial hematoma formation with possibly severe consequences [29]. With the population of patients on novel anticoagulation medications growing, a shift towards more peripheral and superficial nerve blocks may be seen and attention to such RCTs may rise.

With a push towards fast-track and day-case surgery with early mobilization strategies, nerve blocks that provide near-zero pain scores also cause a new burden – the concomitant motor block. An extensive motor block can cause a reduction in patient satisfaction, delay of mobilization and even put patients at risk of falls [30,31]. As an example, excellent analgesia can be achieved by combining a femoral, sciatic and obturator nerve block in total knee

arthroplasty. Although a feasible option, this strategy cannot be adopted, as it limits early mobilization goals [32]. For the same reason, a classic femoral nerve block has lost its popularity due to secondary quadriceps muscle weakness and a link with postoperative incidence of falls [33]. As such, the most recent recommendations including those of the PROSPECT group, suggest the application of novel para-sartorial blocks that spare some of the motor branches of the femoral nerve and do not limit early mobilization [34]. However, there is still a limited number of randomized controlled trials that compare these methods to older alternatives. The publication, that is presented in this thesis, aimed to bridge part of this gap by comparing a proximal para-sartorial block in the distal femoral triangle with the intrathecal morphine standard (see the manuscript in section VI.2). More simple alternatives to advanced RA blocks exist. The use of intrathecal morphine (ITM) has been proven to provide good postoperative pain control and is considered by some as a gold standard following cesarean section [35]. However, the use of ITM creates additional risks, including late-onset respiratory depression. This causes a burden of at least 24-hour monitoring after the administration of ITM [36]. Another alternative may be the use of a mix of analgesic, anti-inflammatory and anesthetic agents in local infiltration analgesia (LIA) administered in large joint surgeries such as total knee arthroplasty. However, standards and techniques differ vastly among centers and even individual surgeons making direct comparisons in research difficult.

The optimal duration of analgesia is still a shortcoming of single-shot nerve blocks. Although, longer analgesia is obtained by choosing a long-acting local anesthetic such as bupivacaine, it is still limited and may result in pain during the suboptimal night hours. The appearance of rebound pain, a phenomenon that is still not fully explained, is the hallmark at the end of the analgesia cover of a peripheral nerve block following pain-inducing surgery [37]. Three main methods try to overcome this limitation: continuous catheter nerve blocks, slow-release formulations like liposomal bupivacaine, and the use of adjuvants to optimize the block characteristics. Continuous catheter techniques have their limitations such as difficulty in placement, specialist equipment required, and a high incidence of secondary failure that is caused in part by catheter dislodgement. Slow-release formulations have not found their way into popular use due to the high expense, relatively few research trials showing any clinical benefit and long implementation procedures for the drug into the market. The most popular remains the use of adjuvants to improve the quality of the RA technique [38]. At present, the

most favorable profile is seen with the steroid dexamethasone providing an additional analgesic and opioid-sparing effect lasting up to 22 hours [39,40]. Intense research has gone into dexmedetomidine, with a recent RCT showing an increase in analgesia duration to 66.3 hours following shoulder arthroscopy when combined with dexamethasone and an interscalene brachial plexus block [41]. However, the limitation of using adjuvants perineurally is the lack of pharmaceutical registration for such use and therefore off-label administration. To overcome this, intravenous dexamethasone has been compared to perineural application and the conclusion showed a slightly less effective result for the intravenous dosage, but still a clinically beneficial extension of the duration of analgesia [42,43]. Other adjuvants have been studied with various side effects noted. Buprenorphine extends the analgesia for 6 hours, but results in a high incidence of nausea and vomiting. Tramadol has also been studied, with conflicting results, and the debate is still open in special circumstances [44]. The aim of our third study (see the manuscript in section VI.3) was to assess a protective and sensory block extension of tramadol in combination with a sciatic nerve block in severe pain-generating calcaneal fracture fixation.

Another shortcoming of blocks of large nerves may be the inadvertent risk of intraneural or even intra-fascicular needle penetration and injection of local anesthetics leading to nerve damage. Although promising, ultrasound guidance is not protective against such a complication [45,46]. The risk of nerve damage increases with poor needle control, performing of nerve blocks under general anesthesia or deep sedation, inadequate teaching and training of RA skills, and implementation of deep blocks into practice [47]. Ways of overcoming the risk have been implemented: dual or triple guidance with the use of ultrasound, nerve stimulation, and injection pressure monitoring reducing the chance of injecting directly into nerve fibers [47,48], improved equipment and techniques of needle tip visualization [49] and awareness of the risk with adequate teaching. However, more distal blocks and fascial plane blocks may reduce the risk of large nerve damage – as the technique itself is based on needling and deposition of local anesthetic at a relative distance from major nerve structures. Another benefit of the distal techniques especially when compared to neuraxial and large plexus blocks is reduced autonomic blockade with better hemodynamic stability. For these reasons, the projects of manuscripts in sections VI.1 and VI.2 may add value to further research. On a

different note, a campaign called “PREP-STOP-BLOCK” has been introduced to prevent wrong side and site blocks [50].

The complexity and novelty of many fascial plane blocks, alterations to classical nerve blocks like the para-sartorial nerve group regional techniques, modes of personalization of regional blocks by use of adjuvants, early mobilization strategies, and ongoing opioid crisis have led to debates on the most optimal analgesic pathways for various surgical procedures. We as authors of the manuscripts, that are part of this dissertation, have created three separate randomized trials to answer part of the debates in chosen clinical scenarios.

V. AIMS OF THE STUDY

The **common aim** of the thesis is the search for optimal methods of postoperative analgesia regimens involving peripheral nerve blocks to overcome certain limitations of regional anesthetic blocks.

The **specific aims** of studies conducted for this thesis:

1. Most optimal fascial plane block for the renal transplant recipient.
2. Consideration of peripheral femoral triangle nerve block as an alternative to intrathecal morphine.
3. Use of a tramadol adjuvant for optimizing the sciatic nerve block following severe pain-generating calcaneal fracture fixation.

VI. COPIES OF PUBLISHED MANUSCRIPTS

VI.1

Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation A randomised trial.

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ORIGINAL ARTICLE

Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation

A randomised trial

Marcin Kolacz, Marcin Mieszkowski, Marek Janiak, Krzysztof Zagorski, Beata Byszewska, Malgorzata Weryk-Dysko, Dariusz Onichimowski and Janusz Trzebicki

BACKGROUND Several studies have shown an analgesic efficacy of a transversus abdominis plane block (TAPB) in reducing opioid requirements during and after cadaveric renal transplantation surgery, but the effect of a quadratus lumborum block (QLB) in this type of surgery is unclear.

OBJECTIVES The main objective of this prospective, randomised, double-centre clinical study was to compare the analgesic efficacy of a one-sided lateral approach TAPB with a unilateral QLB type 2 in cadaveric renal transplantation surgery.

DESIGN Randomised, single-blinded trial.

SETTING Two University-affiliated tertiary care hospitals between April 2016 and May 2017.

PATIENTS A total of 101 patients aged more than 18 years, scheduled for cadaveric renal transplantation.

INTERVENTIONS On receiving ethical board approval and individual informed consent, consecutive patients were allocated randomly to receive either an ultrasound-guided single-shot lateral TAPB or an ultrasound-guided single-shot QLB type 2 on the surgical side using 20 ml of bupivacaine 0.25% with adrenaline after a standardised induction of general anaesthesia. All patients on surgical completion and recovery from general anaesthesia were admitted to the postanaesthesia care unit for 24 h. They received standardised intravenous patient-controlled analgesia with fentanyl, and their pain scores were noted at regular intervals.

MAIN OUTCOME MEASURES The primary endpoint was total cumulative fentanyl dose used per kg body mass in the first 24 h after surgery. Secondary outcomes were the need to start a continuous infusion of fentanyl in addition to patient-controlled analgesia boluses during the stay in post-anaesthesia care unit, postoperative pain severity measured using a numerical rating scale, patient satisfaction with analgesic treatment, evidence of postoperative nausea and vomiting, pruritus and sedation level.

RESULTS The 49 patients allocated to the QLB type 2 group used significantly less fentanyl per kg in the first 24 h after surgery than the 52 patients who received a TAPB (median [IQR] 4.2 [2.3 to 8.0] $\mu g\,kg^{-1}$ versus 6.7 [3.5 to 10.7] $\mu g\,kg^{-1}$, $P = 0.042$). No statistically significant differences were noted in the secondary endpoints within the study, including the frequency of adverse effects of opioids.

CONCLUSION The reduction of fentanyl consumption in the first 24 h after renal transplantation with no difference in pain intensity and patient satisfaction shows a beneficial effect of one-sided QLB type 2 over a one-sided TAPB in regards to postoperative analgesia. However, the reduction in opioid consumption did not affect the frequency of opioid-related adverse effects.

TRIAL REGISTRATION ClinicalTrials.gov ID: NCT02783586.

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From the I Department of Anesthesiology and Intensive Care, Medical University of Warsaw, Warsaw (MK, MJ, KZ, BB, JT) and Department of Anesthesiology and Intensive Care, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland (MM, MW-D, DO)

Correspondence to Marek Janiak, MD, I Department of Anesthesiology and Intensive Care, Medical University of Warsaw, W.H. Lindleya 4, Warsaw 02-005, Poland Tel: +48 22 502 17 21; e-mail: mjaniak8@gmail.com

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Introduction

The mainstay of postoperative pain management following renal transplant surgery is administration of intravenous opioids with the option of using patient-controlled analgesia (PCA) pumps.[1] However, for patients requiring renal transplantation with multiple co-existing morbidities and at risk of delayed graft function, postoperative systemic opioids alone may be inadequate for pain control, and impaired renal function can result in decreased systemic clearance, potentially causing severe adverse effects.[2,3] Other pain management options following renal transplant surgery are limited by the patient's pre-operative comorbidities and by the functional state of the implanted renal graft. Traditional postoperative regional techniques used after renal transplant surgery were based on thoracic epidural analgesia.[4] However, in recent years there has been a shift towards interfascial blocks in postoperative pain management following laparotomy and intra-abdominal laparoscopic procedures, in part due to their reported safety profile and relative simplicity.[5]

Transversus abdominis plane block (TAPB) is used as part of multimodal analgesia protocols in abdominal surgery,[6–8] including renal transplantation.[9–11] Quadratus lumborum block (QLB) is another truncal block for analgesia following abdominal surgery. Many alternative methods of using this block have been reported, depending on the location of local anaesthetic deposition. In type 2, also called a posterior approach QLB, the local anaesthetic is infiltrated on the posterior aspect of the quadratus lumborum muscle beyond the middle layer of the thoracolumbar fascia in an area of the lumbar interfascial triangle.[12] The exact mechanism of action of QLB is still not clear, but its efficacy has been documented.[13–15] When compared with the TAPB, a QLB has been shown to reduce opioid requirements in the postoperative period following lower abdominal surgery in a number of randomised clinical trials.[14,16–18] However, the role of QLBs in renal transplantation surgery remains unclear. The main goal of this study was to assess whether a type 2 QLB on the surgical side would be more effective in reducing opioid consumption than an ultrasound-guided lateral approach TAPB.

To assess this hypothesis, we compared these two blocks in a prospective randomised double-centre clinical study. The primary outcome measure was the total dose of fentanyl used by patients per kg body mass in the first 24 h after renal transplantation surgery.

Methods

Ethical approval for this study was provided by the Bioethical Committee at Medical University of Warsaw, Poland (Chairperson Prof. Zbigniew Wierzbicki) on 15 March 2016 with reference number KB/68/2016. The study was registered at www.clinicaltrials.gov (registration identifier: NCT02783586).

Consecutive patients with an intact anatomy of their urinary outlet, at least 18 years of age, who presented for renal cadaveric transplantation surgery at the two centres (the Department of General and Transplantation Surgery, Medical University of Warsaw and the Department of Transplantology and General Surgery, Voivodal Specialist Hospital, Olsztyn) between 8 April 2016 and 28 May 2017 were considered for the trial.

All patients were instructed on the use of an intravenous PCA pump and on pain intensity rating using a numerical rating scale (NRS) with 0 indicating 'no pain' to 10 defined as 'worst imaginable pain'. Patients considered eligible for the study received an explanation of the study protocol and gave written informed consent for enrolment into the study to a member of the research team.

Exclusion criteria included history of allergy to medications used in the standardised anaesthesia protocol, inability to comprehend or participate in pain scoring, inability to use the PCA system, anatomical or postoperative deformations in the area of the truncal blocks that could possibly affect the spread of local anaesthetic, and any medical condition which could cause an inability to provide informed consent for the study. Each patient was examined by ultrasound to help visualise the transversus abdominis plane as well as the quadratus lumborum muscle. Inability to identify these structures during the initial assessment would exclude the patient from the study protocol. Patient demographic details such as age, sex, height and weight were collected.

Patients meeting the inclusion criteria were randomised using a 1 : 1 allocation to receive either a TAPB or a QLB type 2 with 20 ml of bupivacaine 0.25% and adrenaline 5 μg ml^{-1} (Marcaine-Adrenaline 0.5%; Astra Zeneca, Cambridge, UK) on the side of surgery. A randomisation plan was generated by an online system (Dallal GE. http://www.randomization.com retrieved on 7 March 2016) with permuted blocks (block sizes: 20, 20, 24, 40). Access to the randomisation plan was limited to two study officials. Their role was to inform the specialist in anaesthesiology to which intervention group the included patient was assigned and this information was made available within 1 h prior to the time of the block placement.

All patients enrolled in the study received a standardised anaesthetic regimen. When patients arrived in the operating room, monitoring of heart rate, non-invasive blood pressure, continuous ECG, arterial oxygen saturation and end-tidal carbon dioxide measurements started. Central venous access was obtained in all patients after induction of general anaesthesia, which followed a standard technique with preoxygenation on 100% oxygen for 3 min, intravenous induction with fentanyl (Fentanyl WZF; Polfa Warszawa, Warsaw, Poland) 100 μg, propofol 2 to 3 mg kg^{-1} (Propofol 1% MCT/LCT Fresenius; Fresenius Kabi, Bad Homburg, Germany) and cisatracurium bromide 0.1 mg kg^{-1} (Nimbex; GlaxoSmithKline, Brentford,

UK). Routine tracheal intubation was performed. Anaesthesia was maintained with sevoflurane (Sevorane; AbbVie, North Chicago, Illinois, USA) with 50% oxygen mixture in air aiming for a minimal alveolar concentration of 1.0. Additional boluses of fentanyl and cisatracurium were given during surgery. All patients received intravenous ondansetron 0.1 mg kg^{-1} (Ondansetron; Accord Healthcare, Middlesex, UK) prior to induction of anaesthesia. Before skin incision, intravenous paracetamol 1 g (Perfalgan; Bristol-Myers Squibb, New York, New York, USA) was administered and thereafter repeated every 6 h during the study observation time. At the end of surgery, patients received intravenous neostigmine (Polstigminum; Teva Pharmaceuticals, Warsaw, Poland) for neuromuscular reversal at doses of 50 μg kg^{-1} if needed. On recovery from anaesthesia, additional intravenous fentanyl doses (25 μg every 2 min) were administered if needed to achieve initial postoperative analgesia with NRS 0 to 3. Total anaesthesia time was noted.

After induction of general anaesthesia, with the patient in a supine position, a TAPB or QLB type 2 was performed with adherence to strict aseptic precautions using an echogenic needle (Ultraplex 360 22 gauge; 50 or 80-mm needle, B.Braun, Melsungen, Hessen, Germany). Both methods were performed by trained specialists in anaesthesiology with experience in placing such blocks prior to this study (MK, MM, MJ). All the procedures were under ultrasound guidance using a linear probe or, if unable to identify the appropriate structures, using a curvilinear probe (Toshiba Xario XG with 7.5 MHz linear probe or 3.5 MHz curvilinear probe; BK Flex Focus 400 BK Medical Ultrasound with a 6 to 12 MHz linear probe or 2.5 to 6 MHz curvilinear probe). The patient remained unaware of the allocation group throughout the observation period during the study.

To perform the QLB, the ultrasound probe was placed in the anterior axillary line between the subcostal margin and the iliac crest in the short axis view. On identification of the three muscular layers (external oblique, internal oblique and transversus abdominis muscle), the probe was moved posteriorly until the posterior margin of the quadratus lumborum muscle was identified. A needle was inserted in-plane aiming for the posterior side of the quadratus muscle. The correct position of the needle was confirmed by injecting small aliquots of 2 to 5 ml of 0.9% saline. On proper positioning of the needle tip, 20 ml of bupivacaine 0.25% solution with 5 μg ml^{-1} of adrenaline was administered with visualisation of adequate spread on the ultrasound image.

The TAPB was performed using, initially, the linear probe placed in the anterior axillary line between the subcostal margin and iliac crest. Similarly to the QLB, the three muscular layers were identified but the probe was moved posteriorly only to the level of the mid-axillary line. The needle was inserted from medial to lateral using an in-plane technique that is parallel to the long axis of the probe. Proper needle tip position was identified by hydrodissection with 2 to 5 ml of 0.9% saline. With adequate needle positioning, 20 ml of bupivacaine 0.25% with 5 μg ml^{-1} of adrenaline was administered under ultrasound guidance with appropriate spread assessed during the injection.

In the postoperative period, all patients were admitted to the postanaesthesia care unit (PACU) with standard monitoring and intravenous PCA started (fentanyl, demand dose 30 μg and lockout time of 5 min; 4-h limit 800 μg). Patients who requested additional analgesics, independently of the NRS score, were started on a continuous infusion of fentanyl (titrated to adequate analgesia with infusion rates of 10 to 60 μg h^{-1}) as a background infusion with the PCA boluses.

Total fentanyl consumption during the first 24-h period after surgery was noted. This included the subgroup of patients requiring a continuous infusion regimen for adequate analgesia. The presence of nausea, vomiting and pruritus was assessed by an investigator blinded to the group allocation. Severity of pain during rest and on movement using the NRS with the level of sedation was recorded 1, 6, 12 and 24 h after completion of surgery. Dynamic pain scores were assessed with a trial to sit up in bed or a single cough. The sedation level was based on a simple scale: 1, responds to normal verbal communication; 2, drowsy but responds to verbal communication; 3, asleep but awakens with mild physical stimulus; and 4, asleep and unresponsive to simple physical stimulus. At the time of discharge from the PACU, patients were asked to evaluate their satisfaction with the analgesia regimen using a simple scale: 1, very satisfied; 2, satisfied; 3, dissatisfied and 4, very dissatisfied.

Statistical analysis

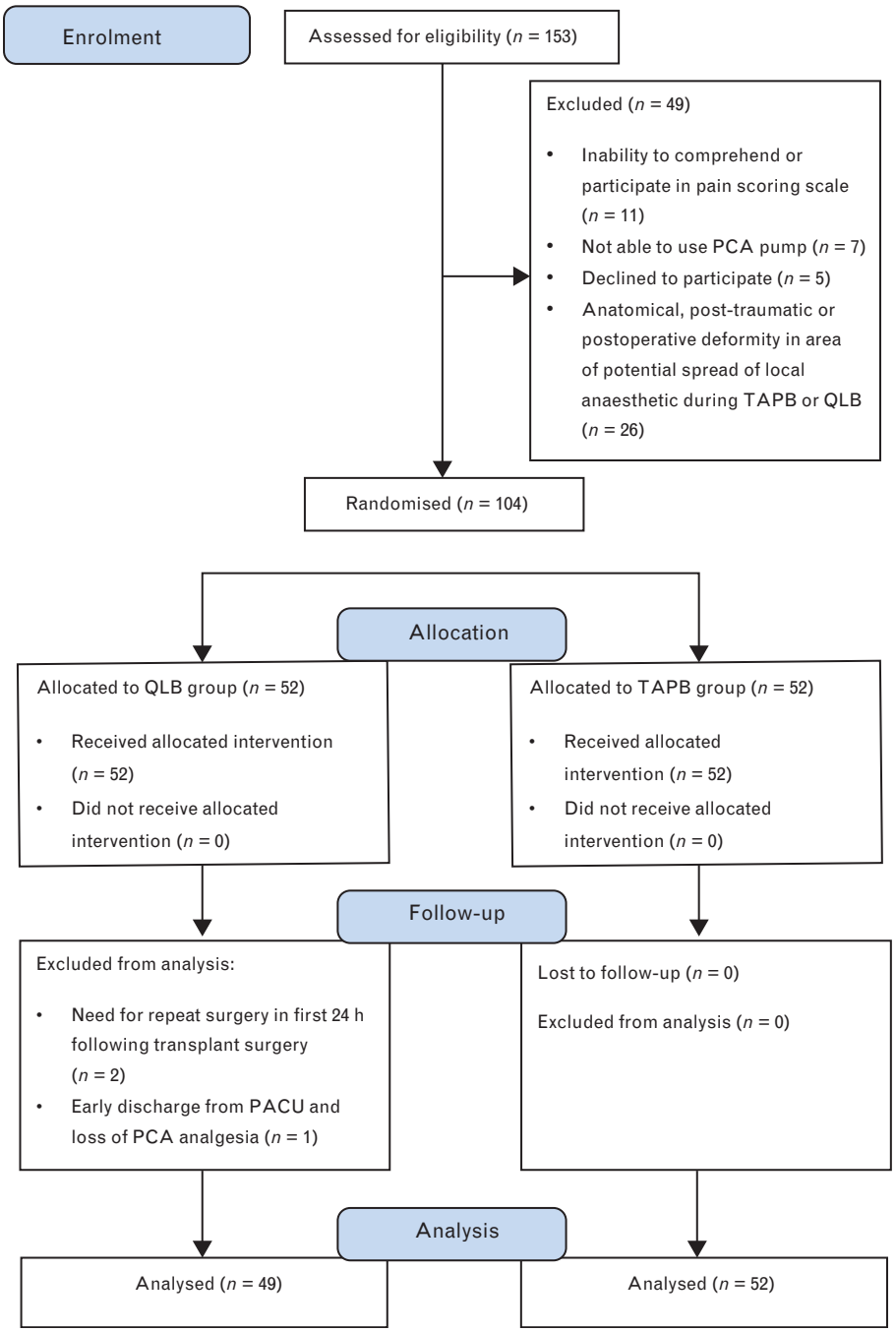
The sample size was calculated according to our prior institutional observations in which the mean ± SD fentanyl requirement of patients after renal transplantation surgery who received a TAPB was 800 ± 350 μg from the time of skin incision. On the assumption that a QLB type 2 would decrease the fentanyl requirements in the first day by 25% when compared with a TAPB with the power of the study set to 0.8, the estimated sample size required was calculated as 96 patients, that is 48 per group. The estimation was calculated using an internet-based software (Kane SP, sample size calculator available on clincalc.com accessed on 25 February 2016). Type I error associated with the test for null hypothesis was assumed to be 0.05. To allow for possible dropouts during the postoperative period, a total of 104 patients was planned with 52 patients per group. Initial data were collected on a standardised protocol form and entered into a computer as numerical or categorical data. All statistical analyses were carried out using the SPSS Statistics programme for Windows (Version 20.0; IBM Corp., Armonk, New York,

USA). Data were assessed for normal distribution based on the Shapiro–Wilk normality test. Qualitative outcomes are presented as percentages and compared using the Fisher's exact test. Quantitative data are presented either as mean ± SD or as median [IQR]. The Mann–Whitney *U*-test was used to assess the differences between groups with non-normal distribution.

Results

The clinical trial was conducted from 8 April 2016 to 28 May 2017. The flowchart according to the CONsolidated Standards of Reporting Trials statement is summarised in Fig. 1. A total of 153 patients were assessed for the study; 49 patients were excluded and 104 patients were allocated randomly into one of two equal groups. Three

Fig. 1



CONSORT study flow chart. CONSORT, CONsolidated Standards Of Reporting Trials; PACU, postanaesthesia care unit; PCA, patient-controlled analgesia; QLB, quadratus lumborum block; TAPB, transversus abdominis plane block.

Table 1 Patient demographics and peri-operative data

	Total, $n = 101$	TAPB group, $n = 52$	QLB type 2 group, $n = 49$
Age (years)	48.6 ± 14.8 51 [35 to 62]	47.5 ± 14.9 49.5 [32 to 61]	49.8 ± 14.7 55 [38.5 to 62]
Male sex	57 (56.4%)	27 (51.9%)	30 (61.2%)
BMI ($kg\,m^{-2}$)	28.2 ± 5.9 27.7 [25.2 to 30.7]	24.7 ± 4.3 23.9 [21.5 to 27.9]	26.1 ± 4.4 26.7 [23.1 to 29]
Intubation-to-extubation time (min)	172 ± 54 165 [138 to 201]	169 ± 55 165 [140 to 187.5]	175 ± 53 170 [135 to 205]
Total intra-operative fentanyl consumption ($\mu g\,kg^{-1}\,h^{-1}$)	2.1 ± 0.8 2 [1.5 to 2.4]	2.1 ± 0.8 2 [1.6 to 2.4]	2 ± 0.7 2 [1.5 to 2.5]

Data are mean ± SD, median [IQR] or number of patients (%). TAPB, transversus abdominis plane block; QLB, quadratus lumborum block.

patients from the QLB group were lost in follow-up. Finally, a total of 49 patients in the QLB group and 52 patients in the TAPB group were included in the analysis. Baseline personal and clinical characteristics (pre-operative and intra-operative data) of both groups were well matched and comparable in both groups (Table 1). No direct harm or unintended effects attributed to the truncal blocks were noted during the study.

Patients who received the QLB had a lower total cumulative fentanyl dose used per kg body mass in the first postoperative 24 h compared with the TAPB group: 4.2 [IQR 2.3 to 8.0] $\mu g\,kg^{-1}$ versus 6.7 [3.5 to 10.7] $\mu g\,kg^{-1}$; this represents a 37.2% reduction in the cumulative dose of fentanyl.

Four patients in the QLB group required a continuous infusion of fentanyl for pain control with five patients in the TAPB group switched to a continuous fentanyl infusion thus demonstrating no difference. There were no significant differences between the two groups with regards to measured pain intensity (at rest or on motion). No differences were found between opioid-related side effects such as sedation level in the first postoperative 24 h measured at different time points, nor in nausea and vomiting or pruritus. The patient satisfaction scores with the analgesic treatment were similar in both groups (Table 2).

Discussion

Our study found a reduction in fentanyl consumption in the first 24 h following cadaveric renal transplantation when a QLB type 2 was compared directly with a TAPB. Our results are in line with the 30.4% reduction in morphine use demonstrated by Yousef[17] following hysterectomy when a QLB type 2 was performed in comparison with a TAPB. Blanco *et al.*[14] demonstrated a lower morphine consumption in women with a QLB type 2 in the first 12, 24 and 48 h after elective caesarean section compared with a TAPB by 37.5, 55 and 48% respectively. The greater reduction of opioid consumption could be explained by a larger component of visceral pain following extensive surgery in a caesarean section with the need

Table 2 Postoperative data

	TAPB group $n = 52$	QLB type 2 group $n = 49$	*P*
Total postoperative fentanyl consumption in first 24 h, $\mu g\,kg^{-1}$	6.7 [3.5 to 10.7]	4.2 [2.3 to 8.0]	0.042
Switch to continuous fentanyl infusion with boluses	5 (9.6%)	4 (8.1%)	1
Postoperative pain intensity at rest			
NRS at 1 h	2.5 [1 to 4]	2 [1 to 4]	0.367
NRS at 6 h	2 [1 to 3]	2 [1 to 3]	0.651
NRS at 12 h	2 [1 to 3]	2 [1 to 3]	0.726
NRS at 24 h	2.5 [1 to 4]	2 [1 to 3]	0.321
Postoperative pain intensity on movement			
NRS at 1 h	4 [3 to 5.8]	4 [2 to 5]	0.239
NRS at 6 h	4 [3 to 5]	4 [3 to 5]	0.761
NRS at 12 h	4 [2 to 5]	4 [3 to 5]	0.437
NRS at 24 h	4 [3 to 5]	4 [3 to 5]	0.602
Postoperative sedation score			
At 1 h	2 [2 to 3]	2 [2 to 3]	0.936
At 6 h	2 [2 to 2]	2 [2 to 2]	0.83
At 12 h	2 [2 to 2]	2 [2 to 2]	0.757
At 24 h	2 [2 to 2]	2 [2 to 2]	0.348
Postoperative nausea	12 (23.1%)	8 (16.3%)	0.459
Episodes of vomiting	11 (21.2%)	7 (14.3%)	0.441
Pruritus	4 (7.7%)	0	0.118
Patient satisfaction score	1 [1 to 2]	1 [1 to 2]	0.258

Values are median [IQR] or number of patients (%). TAPB, transversus abdominis plane block; QLB, quadratus lumborum block; NRS, numerical rating scale.

for bilateral blockade, whereas pain secondary to a renal transplantation is in greater part somatic in origin and the main element of visceral pain originates from the vesicourethral anastomosis. The effect of a QLB type 2 on visceral pain may be secondary to spread of local anaesthetic into the paravertebral space, but evidence is sparse and conflicting.[19–21]

Cadaveric studies demonstrate that injections posterior to the quadratus lumborum muscle consistently stain the iliohypogastric, ilioinguinal and subcostal nerves innervating the surgical area.[19,21] The iliohypogastric and ilioinguinal nerves are not directly blocked by an ultrasound-guided lateral TAPB due to their anatomical relation to the transversus abdominis plane and spread to the thoracoabdominal L1 nerve is inconsistent, which could explain the advantage of a QLB type 2 in cadaveric transplant surgery.[5,22]

Pain intensity using a NRS at rest and on movement was also assessed in our study at 1, 6, 12 and 24 h following the renal transplantation procedure, but no significant difference between groups was demonstrated. A systematic review by Malla *et al.*[23] demonstrated a difference in NRS only in the first hour following abdominal surgery, but no difference was shown at 2, 4, 6, 12 or 24 h postoperatively, whereas Yousef[17] demonstrated a difference in Visual Analogue Scores at 30 min and 2, 4, 6, 12 and 24 h after hysterectomy, which could be explained by more extensive abdominal surgery when compared with a renal transplant surgery. Blanco *et al.*[13] showed a difference in pain scores in favour of a QLB type 2 by calculating the area under the curve in a 48-h postoperative time interval, but our focus was on the first 24 h following surgery due to an intense and diverging care pathway of renal transplant patients.

During our study, only nine patients in total required conversion to a continuous infusion of fentanyl in the postoperative period, which suggests that PCA using fentanyl boluses in combination with a regional block in the form of either TAPB or QLB type 2 is effective in pain management following renal transplant surgery.

A secondary outcome that was assessed included occurrence of opioid-related side effects such as pruritus, nausea and vomiting. Although the occurrence was less frequent in the QLB type 2 group with a mean difference of 6.8% for nausea, 6.9% for vomiting and 7.7% for pruritus when compared with the TAPB group, these differences were not significant. When compared with other studies, no nausea and vomiting was reported following laparoscopic bariatric surgery or total abdominal hysterectomy in the group of patients with a truncal field block.[16,17] No difference was observed in sedation scores at 1, 6, 12 and 24 h between the two studied groups and sedation levels were low throughout. This is in line with the report by Shafeek *et al.*[16] After 24 h of observation in the postoperative unit, all patients in our study were assessed for satisfaction with the pain management following surgery using a questionnaire. Patients from both groups reported good or very good levels of satisfaction with no differences (1 [1 to 2], $P = 0.258$).

Authors of the present study performed the TAPB using the most popular lateral technique,[5] whereas the QLB type 2 was selected for its high ultrasonographic resolution and safety due to the superficial point of injection in relation to other QLB types.[13] Both blocks can be performed in the supine position with the patient under general anaesthesia, reducing the need for moving an unconscious patient.

Complications following truncal blocks are rare and none occurred in our study. The needle trajectory directed towards the posterior wall muscles which we used to perform the QLB type 2 may reduce the risk of intraperitoneal organ puncture, but it is obligatory to visualise the needle tip advancement during performance of the block. Our study showed a reduction in fentanyl consumption with no statistical difference in opioid-related side effects or patient satisfaction which makes TAPB an alternative to QLB type 2 in cadaveric renal transplant surgery when there is insufficient experience in deeper block placement or there are difficulties in visualising the quadratus lumborum muscle in an ultrasound scan. However, the reduction in total cumulative fentanyl consumption with the tendency towards lower incidences of pruritus, nausea and vomiting makes the QLB type 2 in experienced hands a more beneficial block. Further prospective randomised trials in this patient population are warranted.

There are some limitations to our study. QLB type 2 is a fascial plane block in which local anaesthetic is deposited at the posterior edge of the quadratus lumborum muscle blocking the thoracolumbar nerves. However, the exact mechanism of action of this block remains unknown. The ultrasound-guided lateral TAPB has been examined in multiple trials with variable results and there is debate about its effectiveness when multimodal analgesia is used.[5] The major limitation of this study is the lack of block assessment because both TAPB and QLB type 2 were performed after the induction of general anaesthesia and therefore a dermatomal level of blockade check was not possible. In addition, we did not assess the block levels postoperatively due to time constraints and staffing protocols related with transplant surgery. All patients in our study had formal training in the use of a PCA pump prior to surgery, but we did not assess the presence of preoperative chronic pain that may have had an impact on postoperative opioid consumption. We did not measure the serum concentrations of bupivacaine following the truncal blocks. This may be of importance in patients for renal transplant surgery because of poor renal function. However, patients with severe renal impairment demonstrate reduced clearance of local anaesthetics with

increased α_1-acid glycoprotein concentration, resulting in unchanged free plasma concentrations, and dose reductions are not usually required.[24] Well tolerated levels of ropivacaine in the serum with QLBs have also been demonstrated in the study by Murouchi *et al.*[25]

The analgesic efficacy of the truncal blocks in our study was assessed by our primary endpoint, total cumulative opioid use, which is an indirect method of estimating block efficacy. However, a significant decrease in opioid requirements *per se* might not be sufficient to declare QLB type 2 superior to TAPB.[26] A tendency to a lower incidence of opioid side effects was seen, but this was not significant.

Conclusion

The results of our study show a reduction in cumulative fentanyl consumption in the first 24 h following renal transplant surgery which is a beneficial effect of the QLB type 2 over the TAPB. This places the QLB type 2 as a favourable block in comparison with the TAPB even though no statistically significant difference was demonstrated in pain intensity scores, frequency of opioid-related side effects or patient satisfaction with postoperative analgesia.

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Presentation: none.

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Efficacy and side effect profile of intrathecal morphine versus distal femoral triangle nerve block for analgesia following total knee arthroplasty: a randomized trial.

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Efficacy and Side Effect Profile of Intrathecal Morphine versus Distal Femoral Triangle Nerve Block for Analgesia Following Total Knee Arthroplasty: A Randomized Trial

Marek Janiak [1,*], Rafal Kowalczyk [1], Grzegorz Gorniewski [2], Kinga Olczyk-Miiller [1], Marcin Kowalski [3], Piotr Nowakowski [4] and Janusz Trzebicki [1]

[1] 1st Department of Anesthesiology and Intensive Care, Medical University of Warsaw, 02-091 Warszawa, Poland
[2] Department of Anesthesiology and Intensive Care Education, Medical University of Warsaw, 02-091 Warszawa, Poland
[3] Department of Orthopedics and Traumatology, Medical University of Warsaw, 02-091 Warszawa, Poland
[4] Department of Anesthesiology and Intensive Care, Gruca Orthopaedic and Trauma Teaching Hospital, 05-400 Otwock, Poland
* Correspondence: mjaniak8@gmail.com; Tel.: +48-22-502-1724

Abstract: (1) Background: The management of postoperative pain after knee replacement is an important clinical problem. The best results in the treatment of postoperative pain are obtained using multimodal therapy principles. Intrathecal morphine (ITM) and single-shot femoral nerve block (SSFNB) are practiced in the treatment of postoperative pain after knee replacement, with the most optimal methods still under debate. The aim of this study was to compare the analgesic efficacy with special consideration of selected side effects of both methods. (2) Materials and methods: Fifty-two consecutive patients undergoing knee arthroplasty surgery at the Department of Orthopedics and Traumatology of the Medical University of Warsaw were included in the study. Patients were randomly allocated to one of two groups. In the ITM group, 100 micrograms of intrathecal morphine were used, and in the SSFNB group, a femoral nerve block in the distal femoral triangle was used as postoperative analgesia. The other elements of anesthesia and surgery did not differ between the groups. (3) Results: The total dose of morphine administered in the postoperative period and the effectiveness of pain management did not differ significantly between the groups (cumulative median morphine dose in 24 h in the ITM group 31 mg vs. SSFNB group 29 mg). The incidence of nausea and pruritus in the postoperative period differed significantly in favor of patients treated with a femoral nerve block. (4) Conclusions: Although intrathecal administration of morphine is similarly effective in the treatment of pain after knee replacement surgery as a single femoral triangle nerve block, it is associated with a higher incidence of cumbersome side effects, primarily nausea and pruritus.

Keywords: knee arthroplasty; intrathecal morphine; femoral triangle nerve block

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1. Introduction

Total knee arthroplasty is a common surgical procedure with an expected increase in the number of cases due to the aging of populations and the increase in obesity [1]. Over 33,000 procedures were performed in Poland in 2019, and the number has been rising since the year 2005, as seen in data from the Polish Central Endoprostheses Database of the National Health Fund [2].

Postoperative pain following total knee arthroplasty is described as moderate to very severe by most patients [3]. It is well documented that postoperative multimodal analgesic therapy using combinations of regional analgesic techniques provides the most optimal postoperative pain control [4], but direct comparisons of different regional blocks

do not provide a definitive answer to which technique is most preferred. To date, no one regional anesthetic technique is recommended above all others for postoperative pain control following total knee arthroplasty [5,6]. Among methods used to combat severe postoperative pain, both intrathecal morphine and femoral nerve blocks have been used. Both methods are simple to perform and have been shown to be effective in pain control but have a differing profile of side effects and reported patient satisfaction [4]. The aim of this study was to compare the analgesic efficacy of intrathecal morphine versus a single-shot distal femoral triangle nerve block with a special focus on the incidence of side effects related to morphine use.

2. Materials and Methods

In line with the Helsinki Declaration, the Bioethical Committee of the Medical University of Warsaw approved the study (number KB/107/2016, Chairperson Prof. Zbigniew Wierzbicki). Consecutive patients scheduled for primary total knee arthroplasty in the Orthopedic Department of the Medical University of Warsaw were included in the trial. All patients meeting the inclusion criteria received information materials prior and were asked for formal consent to participate in the trial. The exclusion criteria were: lack of consent for inclusion in the trial, lack of consent or a contraindication to performing the regional block techniques employed in the trial, American Association of Anesthesiology score (ASA) of IV or V, chronic opioid use, allergy or contraindications to the drugs used in the trial such as paracetamol, metamizole or ketoprofen.

The trial participants were anesthetized in a block room using a standardized procedure, as per the routine used for knee arthroplasty in our clinical center. Mandatory basic parameters, including an electrocardiogram trace, pulse-oximetry and noninvasive blood pressure, were monitored throughout from the time of admission to the surgical theater area to discharge from the postoperative recovery unit. Allocation to either the intrathecal morphine or distal femoral triangle nerve block was performed using a randomized list known to only one trial coordinator that was not performing the blocks. Due to obvious reasons, double-blinding of the procedure was not fully possible. All the procedures were performed under direct supervision of experienced anesthesiologists. Prior to the anesthetic block, all patients received an intravenous premedication with 0.1 mg of fentanyl (Fentanyl WZF, Polpha, Warszawa, Poland) and 2 mg of midazolam (Midanium WZF, Polpha, Warszawa, Poland). Participants randomized to the intrathecal morphine group (ITM) had a spinal block in the sitting position with 15 mg of 0.5% hyperbaric bupivacaine (Marcaine 0.5% Heavy Spinal, Aspen Pharma Trading Ltd., Dublin, Ireland) and 100 micrograms of intrathecal morphine (Morphini Sulfas WZF 0.1% Spinal, Polfa, Warszawa, Poland). An aseptic technique was used for the intrathecal block in the L3/L4 vertebral interspace using a 26 G atraumatic spinal needle (Atraucan, B. Braun Melsungen AG, Melsungen, Germany). Participants in the single-shot femoral nerve block group (SSFNB) had a distal femoral nerve block within the femoral triangle performed using an aseptic technique under ultrasound guidance with a high linear frequency (12–15 MHz) probe and an 80 mm echogenic block needle (Stimuplex Ultra 360, B. Braun Melsungen AG, Melsungen, Germany). A dose of 20 mL of 0.25% bupivacaine with adrenaline (original solution Marcaine Adrenaline 0.5%, Aspen Pharma Trading Ltd., Dublin, Ireland) was administered on confirmation of sub-sartorial spread lateral to the femoral artery, just as it dives under the sartorius muscle. On confirmation of sensory block with a decrease in sensation to cold in the front peripatellar thigh region, an intrathecal block was performed in the same way as the ITM group, but no intrathecal morphine was administered. Participants in both groups had their spinal block assessed using the Bromage scale and, on confirmation of spinal block effectiveness, were transferred to the operating theater.

The surgical procedure was performed by the same surgical team comprising two orthopedic specialists, with a standardized surgical procedure using a medial peripatellar approach, sacrificing the cruciate ligaments and using bone cement for prosthesis fixation. In all cases, a tourniquet was used to optimize surgical conditions and reduce intraoperative

blood loss which was deflated prior to wound closure. Antimicrobial perioperative prophylaxis and thromboprophylaxis with low molecular weight heparins were implemented in all participants of the study as per hospital protocol.

Monitoring of vital parameters was continued throughout the surgical procedure with intravenous fluid therapy given at the discretion of the anesthesiologist, and in individual cases of patient discomfort, moderate sedation with propofol was used. Following the surgical procedure, all patients were transferred to the postoperative care unit (PACU), where they were monitored for a 24 h period, after which they were discharged to the orthopedic ward. Postoperative analgesia was standardized, with regular intravenous paracetamol 1 g every 6 h and ketoprofen 100 mg every 12 h. All patients had rescue morphine at 0.1 mg/kg administered intravenously on demand under nurse-controlled analgesia every 6 h whenever the Numerical Rating Score (NRS) was more than 4. Vital parameters were recorded every hour. Additionally, trial participants were asked to assess their pain and side effects, such as nausea, vomiting and pruritus, at 1, 6, 2, 24, 48 and 72 h following surgery. At these time points, the nurse also recorded vital parameters and sedation levels. If required, additional doses of morphine and intravenous ondansetron 4 mg were administered. Pain was assessed at all time points using the Numerical Rating Score (NRS) from 0 (no pain) to 10 (worst possible pain) both at rest and with active knee flexion of the operated side. Urinary retention was not assessed as study participants had urinary catheterization.

Statistical analysis of the obtained data was performed using Statistica 13.1 (StatSoft Inc., Tulsa, OK, USA). The data is described using mean values and standard deviations as a measure of dispersion in the case of continuous values or cumulative values for non-continuous data. Comparison of measured variables between groups was performed using the student *t*-test for the parametrical data and the U Mann–Whitney test for the non-parametric data. A normality test by Kolmogorov–Smirnov was performed. For non-continuous data sets, the Chi2 test was used to compare variables. A statistically significant value of $p < 0.05$ was used. A post-hoc power analysis showed the power to be >90% for most variables, such as nausea or pruritus, when considering the sample size.

3. Results

A total of 52 participants were enrolled in the study, with 26 per group. The two groups did not differ in their basic characteristics such as sex, age, anthropometry, ASA classification or duration of surgery, as can be seen in Table 1.

Table 1. Patient characteristics.

	ITM Group	SSFNB Group	*p* Value
Sex Female/Male (%)	23/3 (88.5%/11.5%)	23/3 (88.5%/11.5%)	$p = 1$ (Chi2)
Age (years)	68 +/− 11.9	67.5 +/− 9.7	$p = 0.86$ (*t* test)
Height (cm)	161.2 +/− 6.4	161.5 +/− 6.4	$p = 0.85$ (*t* test)
Weight (kg)	82.2 +/− 15.1	81 +/− 16.6	$p = 0.78$ (*t* test)
Surgical procedure time (min)	87.6 +/− 17.7	92.9 +/− 29.4	$p = 0.43$ (*t* test)
Tourniquet time (min)	72.5 +/− 11.9	73.1 +/− 21.9	$p = 0.9$ (*t* test)
ASA 1/2/3 (%)	1/25/0 (3.8%/96.2%/0)	0/24/2 (0/92.3%/7.7%)	$p = 0.36$ (Chi2)

Values are presented as mean +/− SD or as number/percentage. ASA—American Society of Anesthesiology physical status scale. ITM = intrathecal morphine, SSFNB = single-shot femoral triangle nerve block.

Table 2 shows the results of the assessed variables between the ITM and SSFNB groups. The cumulative morphine dose did not differ between the two groups in the 72 h observation period. A statistically and clinically relevant reduction in nausea and pruritus could be seen in the postoperative period in the femoral triangle nerve group. Both pruritus and nausea occurred in at least half of the group that received the intrathecal morphine but were a rare occurrence in the femoral nerve block group. More patients required the

administration of ondansetron in the postoperative period in the ITM group, and this was statistically significant. The effectiveness of the analgesic regimen did not differ between the two groups in terms of the NRS results (Tables 3 and 4). A benefit of the femoral nerve block was noted at some time points, such as at six postoperative hours at rest ($p = 0.0361$) and on discharge from the PACU when NRS was assessed on knee flexion ($p = 0.0138$).

Table 2. Treatment results.

	ITM Group	SSFNB Group	*p* Value (Statistical Test)
Cumulative morphine dose (mg)	31 [23–37]	29 [23–31]	$p = 0.26$ (U Mann–Whitney)
Nausea N (%)	13 (50%)	2 (7.7%)	$p = 0.0008$ (Chi2)
Vomiting N (%)	7 (26.9%)	1 (3.8%)	$p = 0.211$ (Chi2)
Pruritus N (%)	14 (53.8%)	1 (3.8%)	$p = 0.0001$ (Chi2)
Somnolence N (%)	15 (57.7%)	9 (34.6%)	$p = 0.09$ (Chi2)
Maximum NRS at rest	4 [2–5]	2 [0–6]	$p = 0.18$ (U Mann–Whitney)
Maximum NRS on motion	4 [3–7]	3.5 [2–7]	$p = 0.22$ (U Mann–Whitney)
Number of patients requiring ondansetron N (%)	13 (50%)	3 (11.6%)	$p = 0.0271$ (Chi2)
Number of patients requiring naloxone N (%)	2 (7.7%)	0 (0%)	$p = 0.1649$ (Chi2)

ITM = intrathecal morphine. SSFNB = single-shot femoral triangle nerve block. Values x[y-z] signify median[interquartile range].

Table 3. Postoperative pain levels at rest.

NRS at Rest	ITM Group	SSFNB Group	*p* Value (U Mann–Whitney)
On admission to PACU	0 [0–0]	0 [0–0]	$p = 1$
At 3 h	0 [0–0]	0 [0–0]	$p = 0.7418$
At 6 h	3 [0–4]	0 [0–2]	$p = 0.0361$
At 9 h	0 [0–2]	1 [0–3]	$p = 0.602$
At 12 h	1 [0–2]	0 [0–2]	$p = 0.3554$
At 18 h	0.5 [0–2]	0 [0–0]	$p = 0.07$
On discharge from PACU	0 [0–1]	0 [0–0]	$p = 0.1938$

NRS = numerical Rating Score, ITM = intrathecal morphine, SSFNB = single-shot femoral triangle nerve block.

Table 4. Postoperative pain levels on motion.

NRS on Motion	ITM Group	SSFNB Group	*p* Value (U Mann–Whitney)
On admission to PACU	0 [0–0]	0 [0–0]	$p = 0.819$
At 3 h	0 [0–0]	0 [0–0]	$p = 0.7007$
At 6 h	3.5 [0–5]	0 [0–3]	$p = 0.0582$
At 9 h	3 [0–4]	2 [0–4]	$p = 0.7143$
At 12 h	2.5 [1–3]	1 [0–4]	$p = 0.1176$
At 18 h	1.5 [1–4]	1 [0–2]	$p = 0.1242$
On discharge from PACU	1 [1–4]	0 [0–2]	$p = 0.0138$

NRS = numerical Rating Score, ITM = intrathecal morphine, SSFNB = single-shot femoral triangle nerve block.

No relevant complications of the spinal block or the femoral nerve block were noted among the study participants, but two patients required the administration of a small dose of naloxone due to bradypnea with overt sedation in the ITM group.

Intra- and postoperative hemodynamic values of blood pressure, heart rate or oxygen saturation did not differ between the two groups. With the exception of two cases requiring naloxone administration, no desaturations relevant to the study were noted, but it must be

stated that the measurements were recorded at specific time points, and any reduced value of oxygen saturation was treated with oxygen supplementation, which was not recorded.

4. Discussion

We assessed the efficacy of a 100 mcg intrathecal morphine in comparison to a single-shot femoral nerve block performed in the femoral triangle with a sub-sartorial spread just lateral to the femoral artery for postoperative analgesia following total knee arthroplasty. Our study shows that both these methods are equianalgesic and can be used alternatively. However, the undesirable side effect profile of intrathecal morphine must be taken into account, with a potential for a rare but dangerous respiratory depression.

Total knee arthroplasty is an orthopedic procedure commonly performed for gonarthrosis. Although the aim of the surgery is to reduce chronic pain related to knee degeneration [7], pain intensity can be very severe directly after the surgery. Effective analgesia with the use of regional blocks is optimal for fast-track patient mobilization and achievement of good functional recovery of the knee joint [8,9]. It is possible that the use of regional anesthetic techniques could help reduce hospital stay time and the incidence of side effects related to long-term opioid use [10].

A single-shot femoral nerve block is one of the accessible methods of pain management following knee arthroplasty [11]. It does not provide prolonged analgesia with the added flexibility that a continuous femoral triangle nerve block can [12,13], especially when combined with a sciatic nerve block [14], but in comparison to the continuous nerve block, it carries a reduced risk of falls in the postoperative recovery time [15,16]. A study by Wyatt et al. [17] showed no major advantage of a continuous femoral nerve block over a single-shot technique when used in combination with ITM. For these reasons, a single-shot technique with a more distant block area and no sciatic nerve blocking was chosen in our trial to reduce the risk of a fall due to quadriceps muscle weakness in early mobilization. However, we do note that the most recent PROSPECT guidelines on total knee arthroplasty do not recommend any femoral nerve block due to the potential negative impact on functional, fast-track recovery [18], but the study was designed in the time before the focus was placed on the higher risk of falls following total knee arthroplasty and this may still be debatable. No study participant experienced a fall, and femoral nerve block is still used as an analgesic option as local infiltration analgesia (LIA) is not practiced by our orthopedic surgeons.

Single-shot femoral nerve block following total knee arthroplasty is more effective compared to simple local wound infiltration [19]. It has a similar or less effective profile when compared to an adductor canal block which, on the other hand, helps preserve more motor function of the quadriceps muscle of the thigh [20,21]. A shift toward finding more optimal distal motor-sparing blocks is observed in the literature. A novel parasartorial compartment (PASC) block is one such promising alternative [22]. The study by Lee et al. [12] found a comparable analgesic result when a continuous catheter was placed in the femoral triangle in comparison to a proximal and distal adductor canal catheter position.

Morphine administered intrathecally (ITM) has a proven efficacy in the treatment of postoperative pain following large joint arthroplasties [23]. The benefit of ITM is the ease of administration and no additional complications related to the injection itself as compared to the more invasive nerve block procedure. The major drawback of ITM is the high incidence of side effects that are not well tolerated by patients, such as nausea, pruritis and sedation [24]. A potential complication remains late apnea related to post-opioid respiratory center depression [25]. In our study, 2 participants in the ITM group experienced respiratory depression with bradypnea and overt sedation after 15 h and required administration of naloxone with full recovery. No evident drop in saturation was noted as oxygen was being administered, but the apnea triggered a monitor alarm. This is not statistically significant as the study groups are small, but it remains clinically relevant. As the cumulative systemic morphine dose did not differ between the groups, it should be noted that ITM may have caused respiratory depression. No additional factors, such as obstructive sleep apnea, were found to contribute to these cases. The patients remained

in the PACU for the 24 h postoperative period and were discharged to the ward with no further action required.

In both our study groups, undesirable side effects were observed secondary to the implemented analgesia. The incidence of nausea and pruritis was significantly higher in the ITM group, even though the overall opioid consumption was similar in both groups. Our trial results remain in line with a metanalysis which showed an associated increased pruritis and a decreased patient satisfaction [26,27], although no difference in side effect profile was observed in one study [28].

Recommendations pertaining to analgesia for total knee arthroplasty combine paracetamol, non-steroidal anti-inflammatory drugs and opioid therapy [6,9,18]. The used multimodal analgesic regimen in the trial provided good pain management in both study groups.

Our study has several limitations. Firstly, the study was not blinded—both the anesthesiologist performing the block and the patient were aware of the group allocation. However, the personnel assessing the outcomes, including pain scores and side effects, were unaware of the group allocation of the participants. Secondly, our study investigates a femoral triangle nerve block which may be related to quadriceps muscle weakness affecting early mobilization. We did not assess patient satisfaction in the perioperative period.

5. Conclusions

In our randomized trial, the results show a similar overall efficacy of intrathecal morphine at a dose of 100 micrograms to a single-shot femoral triangle nerve block but with a higher incidence of undesirable side effects among patients receiving intrathecal morphine, especially nausea and pruritus. The risk of respiratory depression, which occurred in our study in the intrathecal morphine group, confirms the need for respiratory monitoring and limits its possible safe use in day-case surgery.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study may be available on request made to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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VI.3

Effect of intramuscular tramadol on the duration of clinically relevant sciatic nerve blockade in patients undergoing calcaneal fracture fixation. A randomized controlled trial.

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Effect of Intramuscular Tramadol on the Duration of Clinically Relevant Sciatic Nerve Blockade in Patients Undergoing Calcaneal Fracture Fixation: A Randomized Controlled Trial

Marek Janiak [1,*], Grzegorz Gorniewski [2], Rafal Kowalczyk [1], Piotr Wasilewski [3], Piotr Nowakowski [4] and Janusz Trzebicki [1]

[1] 1st Department of Anesthesiology and Intensive Care, Medical University of Warsaw, 02-005 Warsaw, Poland
[2] Department of Anesthesiology and Intensive Care Education, Medical University of Warsaw, 02-007 Warsaw, Poland
[3] Department of Orthopedics and Traumatology, Medical University of Warsaw, 02-005 Warsaw, Poland
[4] Department of Anesthesiology and Intensive Care, Gruca Orthopedic and Trauma Teaching Hospital, 05-400 Otwock, Poland
* Correspondence: mjaniak8@gmail.com; Tel.: +48-22-502-1724

Abstract: Background: Calcaneal fracture fixation can generate severe postoperative pain and analgesia can be supported by a sciatic nerve block. However, following resolution of the sensory blockade, rebound pain may ensue. The aim of this study was to assess whether an incidental finding of two patients with an extension of the sciatic nerve block beyond 24 h following 100 mg of intramuscular tramadol administration could be confirmed. Methods: Thirty-seven patients scheduled for a calcaneal intramedullary fixation (Calcanail®) were randomly divided into two groups. The tramadol group (n = 19) received a sciatic nerve block with 20 mL of 0.25% bupivacaine and a concomitant dose of 100 mg of intramuscular tramadol, while the control group (n = 18) received an identical sciatic nerve block with concomitant injection of normal saline (placebo). All patients had a spinal anesthesia with light sedation for the procedure. The time to first analgesic request defined as appearance of any pain (NRS > 0) was assessed as the primary endpoint with a clinically relevant expected result of at least 50% elongation in sensory blockade. Results: The median time to first analgesic request from time of blockade in the tramadol group was 670 min compared with 578 min in the control group. The result was clinically not relevant and statistically not significant (p = 0.17). No statistical difference could be demonstrated in the time to first opioid request, although a trend for opioid sparing in the tramadol group could be seen. Total morphine consumption in the first 24 h was also statistically insignificant (the tramadol group 0.066 mg kg^{-1} compared with 0.125 mg kg^{-1} in the control group). In conclusion, intramuscular tramadol does not extend the duration of analgesia of a sciatic nerve block following a calcaneal fracture fixation beyond 2 h and an opioid sparing effect could not be demonstrated in this trial.

Keywords: tramadol; sciatic nerve block; calcaneal fracture fixation

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1. Introduction

Calcaneal fractures may account for only 1–2% of all fractures, but about 71% are intraarticular and most require surgical reduction and fixation for better functional and anatomical recovery [1,2]. However, postoperative pain in the first 24 h following open calcaneal fracture surgery has been assessed as the most severe among 179 surgical procedures with a median numerical rating score (NRS) of 6.8 [3]. Hence, it may be prudent to supplement basic anesthesia with a regional block covering the innervation of the hindfoot such as a single-shot sciatic nerve block. The duration of such a block may not ensure pain control for the first 24 h after the procedure and severe rebound pain may ensue. The use of several adjuvants has been proven to extend the duration of the sensory blockade.

Dexamethasone has proven efficacy as an adjuvant to nerve blocks when administered both perineurally and intravenously with at least 1.5 times when compared with nerve block with only local anesthetic [4,5]. Tramadol has been studied as an adjuvant in perineural and systemic co-administration with a nerve block, with inconsistent results to date. No trial assessing the use of intramuscular tramadol in conjunction with a sciatic nerve block is known to the authors of this study.

Based on an incidental finding in our institution of an effective sciatic nerve blockade with over 24 h in two patients following calcaneal fracture repair that received intramuscular tramadol prior to surgery, we designed a randomized trial with the aim to investigate whether tramadol can prolong the sensory blockade by at least 1.5 times for clinical relevance providing the 'overnight' analgesic benefit.

2. Materials and Methods

The prospective single-center, randomized trial was conducted at the 1st Department of Anesthesiology and Intensive Care, Clinical University Centre Hospital, Warsaw, Poland. This trial was approved by the ethics review board of the Warsaw Medical University (Approval number KB/128/2017, Chairperson Prof. Zbigniew Wierzbicki) and registered with data safety authorities with study registry under ClinicalTrials.gov, NCT03477851. The study protocol complied with the principles laid down in the Declaration of Helsinki and the CONSORT 2010 Statement. All study participants provided written informed consent to participate in the trial.

We enrolled consecutive patients from August 2017 till October 2020. A considerable delay in recruitment was caused by a relative rare occurrence of calcaneal fractures suitable for intramedullary nailing and due to the COVID-19 pandemic. Adults aged more than 18 years undergoing intramedullary nail implantation for a calcaneal fracture were eligible for participation. Exclusion criteria were as follows: a history of allergy to local anesthetics and analgesics used in the study, any contraindication to the sciatic nerve block such as infection at the puncture site, chronic opioid use, any contraindication to the intramedullary nailing technique, use of tramadol before the procedure, and inability to obtain or lack of consent for inclusion in the study.

Patients were randomly assigned in a 1:1 ratio to receive either 100 mg tramadol intramuscularly (tramadol group) or normal saline intramuscularly (control group). The random allocation sequence was generated by a single research assistant (Grzegorz Gorniewski) before the start of participant recruitment with sequentially numbered, opaque, and sealed envelopes. Prior to sciatic nerve block, identical syringes were prepared by the single research assistant (Grzegorz Gorniewski) not directly involved in patient care in a manner blinded to other participants of the study. All participants, attending anesthesiologists and outcome assessors were not informed of the group allocation.

2.1. Anesthetic Procedure and Intervention

No premedication was administered prior to arrival in theatre. Standard monitoring included electrocardiography, peripheral pulse oximetry and noninvasive blood pressure (NBP) measurement. Intravenous midazolam (Midanium, Polfa Warszawa, Warsaw, Poland) of 1 to 3 mg was administered to patients after confirming consent for the procedures and study inclusion. All participants received a spinal anesthesia with hyperbaric bupivacaine 10–15 mg (Marcaine Spinal 0.5% Heavy, Aspen Pharma Trading Limited, Dublin, Ireland). Pre-emptive analgesia with intravenous Paracetamol 1 g (Paracetamol Kabi Deutschland GmbH, Friedberg, Germany) was started at the time of performing the spinal anesthesia. Following onset of the spinal block, a single-shot sciatic nerve block was performed in the popliteal region at the division of the tibial and common peroneal nerve. The patient's lower limb was flexed at the hip and knee joint to obtain access to the popliteal area and a linear 8–12 MHz transducer was used to identify the point of injection. Under sterile conditions, an 80 mm 22-gauge needle (Stimuplex D, B. Braun Melsungen AG, Melsungen, Germany) tip was positioned in-plane initially under the point of division of

the sciatic nerve with the aim to spread the solution inside the perineural membrane of the sciatic nerve. On confirmation of appropriate spread a total of 20 mL of 0.25% bupivacaine was injected. All sciatic nerve blocks were performed by experienced anesthesia providers (Marek Janiak, Rafal Kowalczyk).

Patients randomized to the active treatment group received an intramuscular injection with 100 mg of tramadol (Poltram 100, Polpharma S.A., Starogard Gdanski, Poland) and patients in the control group received a similar volume of normal saline solution intramuscularly. The injections were performed into the non-operated lower limb that was blocked by the spinal anesthesia making it pain-free. The spinal anesthesia was performed in all cases from a sitting position, followed by an immediate supine patient placement and therefore the hemodynamic effects of the spinal block on both limbs were considered equal. Intramuscular tramadol absorption can be assumed to be identical and independent in which lower limb the drug was administered.

Postoperatively, all patients had intravenous paracetamol 1 g continued every 6 h starting from the pre-emptive dose and metamizole (Pyralgin, Polpharma S.A., Starogard Gdański, Poland) 1 g every 6 h beginning at block resolution (Numerical Rating Score, NRS > 0). Morphine hydrochloride was administered at doses of 1 mg kg^{-1} (but not more than 10 mg) every 4 to 6 h beginning with a NRS > 3 and continued as nurse-controlled analgesia (NCA).

2.2. Intramedullary Nailing

Before surgery, all patients received a single dose of preoperative antibiotic prophylaxis (1.5 g cefuroxime intravenous). Positioning of the patient for the surgery was supine with the operated limb placed outside the surgical table on a strut. The surgical procedure was performed by the same technique and by the same experienced surgical team (Piotr Wasilewski) using a dedicated calcaneal nail set (Calcanail®, FH Orthopedics, Heimsbrunn, France), making the surgery standard for all patients in this study. No wound drains were required, and no additional cast was needed.

2.3. Study Endpoints

The primary endpoint was the time to first sensation of pain in the operated limb (NRS > 0). The participants and nursing staff were asked to note the time of first pain. This request was made at several points of the study: at the moment of taking consent for the trial, at arrival to the theatre, and on transfer to the postoperative unit.

Secondary outcomes were time to first request for morphine (NRS > 3), total 24 h morphine consumption, and total time of sensory block. The total analgesic requirements were taken from the patients' medical charts.

2.4. Statistical Analysis

Our sample size calculation was based on an expected block prolongation of at least 50% making it clinically meaningful. This would lead to an extension of a pain-free period of at least 2 to 3 h. Any shorter time to first pain would not be considered clinically relevant. According to our power analysis (alpha = 0.05 and beta = 0.9), a sample size of 18 participants was required.

Statistica 13 (Dell Incorporated, Tulsa, OK, USA) was used for the statistical analysis. All variables were tested for normality of distribution via the Shapiro–Wilk test. Parametric variables were reported as mean ± SD and non-parametric variables as median [IQR] with comparison between groups made by a student *t*-test or a Mann–Whitney U test. Categorical data were reported as number (proportion in percentage) with comparisons evaluated using the chi square test. A p value of less than 0.05 was considered statistically significant. Kaplan-Meier plots and the log-rank test were used because of a significant proportion of censored observations in time to first opioid analysis.

3. Results

Of 43 patients assessed for eligibility, two did not meet the inclusion criteria due to known tramadol intolerance and one declined to participate, leaving 40 for enrolment. One patient in the treatment group retracted the consent due to objection to the intramuscular injection, and two were excluded due to a protocol breach. Finally, 19 participants in the tramadol group and 18 in the control group were included in the analysis. The flowchart according to the CONSORT statement is summarized in Figure 1. There were no complications of the performed blocks and for all the patients, the postoperative period was overall uneventful.

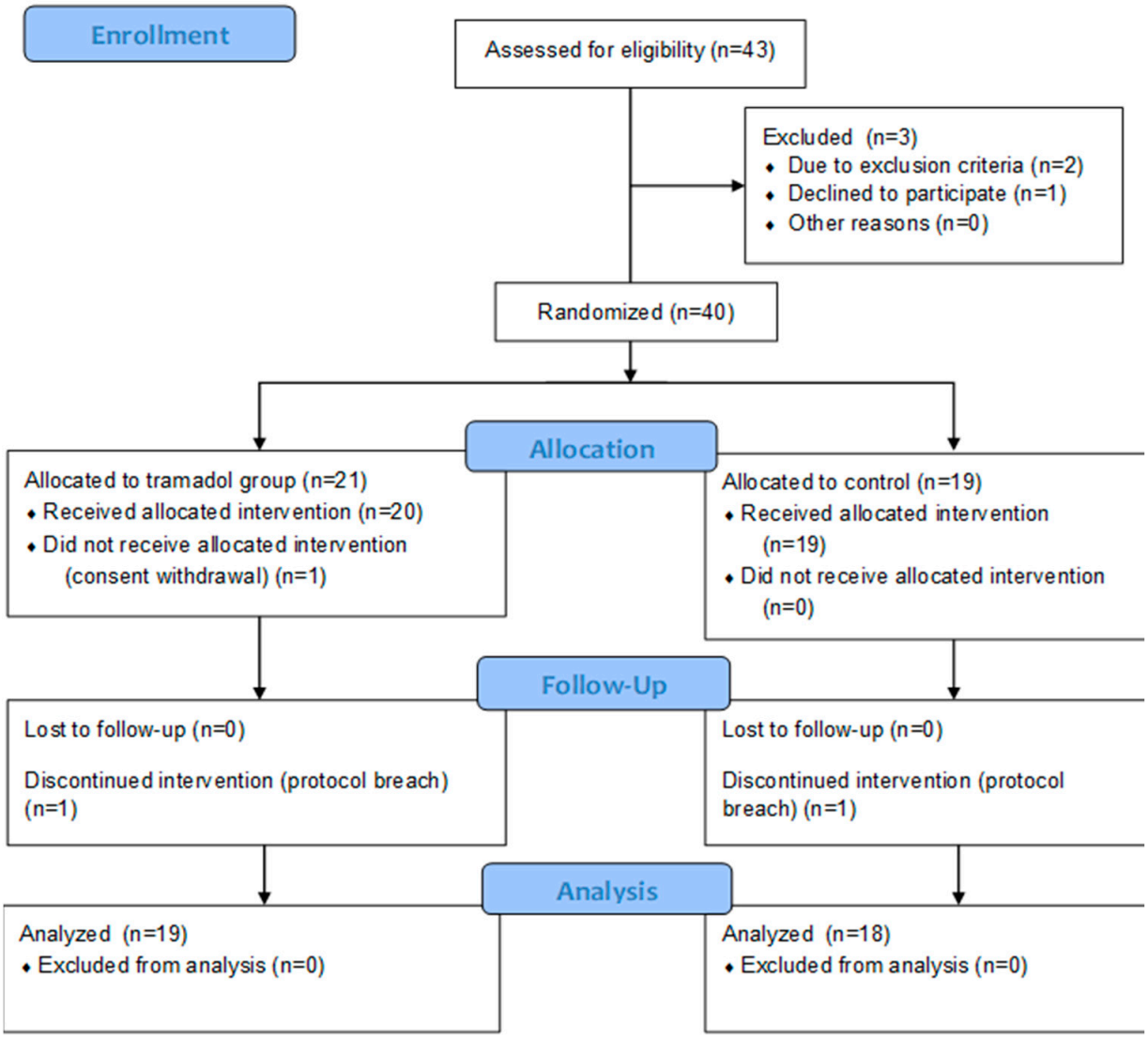

Figure 1. CONSORT flowchart.

The mean age of the patients at the time of surgery was 48 ± 13.3 (ranging from 21 to 80). There were 10 women and 27 men, which were comparably divided between the two groups. Baseline personal and clinical characteristics were comparable between the groups (Table 1), with one patient assessed as American Society of Anesthesiologists' physical status III in the control group. All subjects in the study had a unilateral closed calcaneal fracture, with over 70% having intra-articular involvement. Based on the Sanders classification of calcaneal fractures, the most common type was Sanders A (lateral third two-part fracture), followed by Sanders type B (two-part, central third of calcaneum), which is in line to the results of the study that assessed the epidemiology of 957 of such fractures in

CT scans [1]. In our study, no differences in pain assessment were noted between different types of calcaneal fractures, but this would not be statistically significant due to the number of subjects in the study.

Table 1. Basic demographic characteristics.

Variables	Tramadol Group N = 19	Control Group N = 18	*p* Value
Age (years)	51 ± 10.28 (31–66)	45 ± 15.8 (21–80)	$p = 0.22$ (*t*-test)
Height (cm)	172.2 ± 12.26 (140–189)	171.1 ± 8.11 (169–190)	$p = 0.74$ (*t*-test)
Weight (kg)	77.2 ± 15.22 (57–132)	72.4 ± 12.68 (48–95)	$p = 0.31$ (*t*-test)
ASA physical status (I/II/III)	9/10/0	8/9/1	$p = 0.99$ (Chi2)
Duration of surgery (minutes)	50 [45–55]	58 [50–70]	$p = 0.15$ (Mann–Whitney U)
Sex (M/F)	4/15 (21%/78%)	6/12 (33%/57%)	$p = 0.4$ (Chi2)

Values are reported as mean ± SD, median [IQR] or number (percentage) where appropriate. ASA: American Society of Anesthesiologists.

Significant variability in the duration of the sensory block was seen, ranging from 310 min to over 24 h independent of the group allocation. For the primary endpoint, the median time to first sensation of pain with NRS > 0 was 670 min in the tramadol group and 578 min in the control group. This difference was not clinically and statistically significant ($p = 0.17$, log-rank test) as seen in the Kaplan-Meier plot (Figure 2). No significant difference in the time to first morphine request for an NRS > 3 using the survival analysis with the log-rank test ($p = 0.21$) was observed although a visible trend in favor of the treatment group was noted (Figure 3).

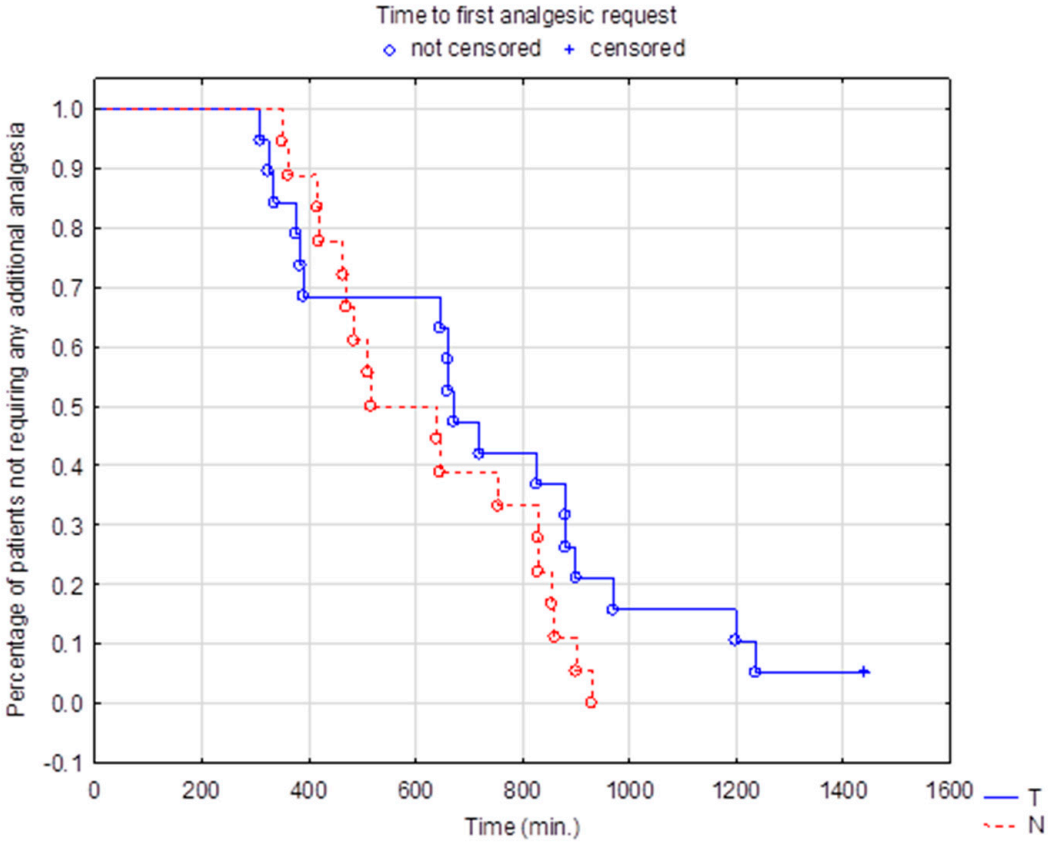

Figure 2. Kaplan-Meier plot for time to first analgesic request for NRS > 0. Blue line (T): tramadol group. Red line (N): control group.

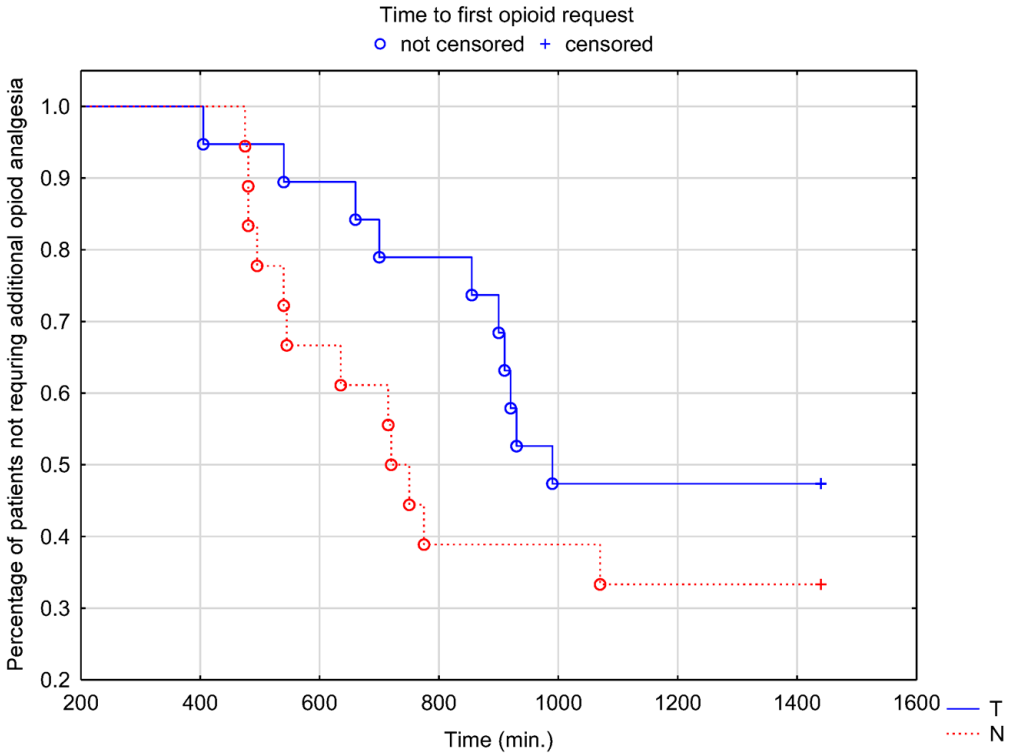

Figure 3. Kaplan–Meier plot of time to first requested opioid for NRS > 3. Blue line (T): tramadol group. Red line (N): control group.

The cumulative morphine consumption in the 24 h following the surgery was assessed with the mean for the tramadol group 0.066 mg kg^{-1} compared with 0.125 mg kg^{-1} in the control group. This difference was found not to be statistically significant ($p = 0.057$ log-rank test).

4. Discussion

In our study, intramuscular administration of tramadol with a single-shot sciatic nerve block did not prolong the duration of the sensory blockade beyond the cutoff time of at least 2 h as measured by the time to first simple analgesia and the first opioid administration, which makes our initial observation of two patients with an extended block an incidental finding. The sciatic nerve block extended the analgesia beyond the spinal block which would suggest that all our study participants had an effective nerve block.

The role of adjuvants in peripheral nerve blocks is to optimize the analgesic properties of the local anesthetic by enhancing the onset of action and extending the duration of the sensory block, thereby decreasing analgesic requirements, especially the cumulative doses of opioids. Several adjuvants, such as dexamethasone and dexmedetomidine, have shown a beneficial effect when administered perineurally, but the exact mechanisms of action are debated. Focus on the possible systemic absorption of such drugs and its effect on other pain pathway points is considered and superiority of perineural over systemic administration is not yet confirmed. Administration of 0.15 mg/kg or 8 mg of intravenous dexamethasone in combination with a peripheral nerve block has provided pain relief for 75% of patients after ankle and shoulder surgery for more than 24 h [6]. A study by Abdallah et al. [7] showed that the alfa 2 agonist, dexmedetomidine, extended the analgesia of an interscalene plexus block to about 10 h compared with the placebo independent of whether administered as a perineural or intravenous adjuvant. Alternative methods of extending the duration of analgesia such as continuous nerve block techniques with the aid of catheters or repeat single-shot nerve blocks are cumbersome and require additional health resources which make the use of pharmacological adjuvants the first choice in present regional anesthesia practice.

Tramadol is not clearly recommended as an adjuvant to nerve blocks as unequivocal evidence for its efficacy is lacking and potential for side effects not negligible with little known on its neurotoxic potential when administered perineurally [5], though it remains a commonly used opioid analgetic in many postoperative settings. A direct local anesthetic effect of tramadol was observed in animal models [8,9] as well as in human volunteers [10], but the evidence for the effect of tramadol on nerve blockade is unclear. It may be important to note that the local anesthetic effect similar to 2% lidocaine was observed when tramadol was administered to a sciatic nerve of a rat and its role as an adjuvant in this setting warranted trial designs similar to ours. No previous trial has been performed evaluating the clinical effect of systemic tramadol as an adjuvant in sciatic nerve blocks in human subjects, making our trial one of the first to transfer the possible results seen in the animal models to a clinical scenario. There exist some evidence of its capability to prolong clinically relevant analgesia when used as a block adjuvant to levobupivacaine [11], lidocaine [12], mepivacaine [13], and ropivacaine [14,15] for different blocks and surgical procedures. Analgesia prolongation with brachial plexus block has been observed with perineural [16] and intramuscular administration [11], but not necessarily with intravenous administration of tramadol [17]. In the study by Alemanno et al., intramuscular tramadol at a dose of 1.5 mg/kg in conjunction with a single-shot interscalene block had a similar effect to the perineural administration and prolonged the time to first analgesia request in patients undergoing an intense pain generating arthroscopic rotator cuff repair [11]. The authors of this trial suggested that some of the conflicting results from other studies may have been due to studies involving tramadol as an adjuvant in surgery generating mild postoperative pain and therefore impairing accuracy in detecting differences between study groups, but in our study the expected postoperative pain levels are high [3]. In a systematic review for tramadol as an adjunct in brachial plexus blocks, the analgesia prolongation effect, although relatively reliable, remained highly heterogenous between the studies and with a median of 125.5 min [16]. Tramadol has been reported to improve analgesia of the periprostatic nerve block during urological procedures [18], inferior alveolar nerve block in endodontic surgery [19].

Sciatic nerve block alone has a relatively long duration of action, with use of 20 mL of levobupivacaine or ropivacaine, depending on concentration its analgesic efficacy effective analgesia lasts for 13 to 19 h with higher concentrations resulting in longer motor and sensory blockade [20]. Similar mean duration was observed for 0.5% bupivacaine of 880 min when it was compared with other local anesthetics such as ropivacaine [21]. The observed median time in the tramadol group of our study of 670 min for the sciatic nerve block was shorter and of considerable variation, which could not be explained by any of the collected variables including the type of the calcaneal fracture. Block duration did not correlate in our study with bupivacaine dose per kilogram of patient body weight.

Opioids are well-studied in preemptive or preventive analgesia although the quality of evidence remains moderate [22]. Tramadol seems to be effective in both settings, with administration of the tramadol before induction of anesthesia resulting in lower total consumption of the analgesic [23,24]. In orthopedic surgery, tramadol with paracetamol seems to be efficient in preemptive or preventive analgesia administered both oral or intravenous [25,26], as well as intraarticular [27] or as subcutaneous wound infiltration [28]. The timing of tramadol administration in our study before the surgical insult was not aimed at assessing the possible preemptive analgesic mechanism, but was based on the standard use of several known and effective nerve block adjuvants such as dexamethasone administered at the time of performing the block itself.

Intramuscular injection is generally not a recommended route for tramadol, but no clear evidence of perineural injection of tramadol over systemic administration has been demonstrated. In our study, patients were not able to feel any pain of injection as spinal anesthesia was performed before the intramuscular injection. The duration of analgesic effect of a single 100 mg tramadol dose is about 6 h after intravenous or

oral administration and the duration of action after intramuscular injection seems to be similar with tramadol administered via an intramuscular injection having a bioequivalent availability as a 30 min intravenous infusion with peak systemic concentration at 1.1 h from the time of administration [29]. The duration of action of intramuscular tramadol alone does not fully explain the observed delay to first opioid analgesic request in our study treatment group, although residual analgesic activity of single 100 mg intramuscular tramadol dose may extend over 6 h [30]. A perineural administration of tramadol was considered prior to trial design, but at the time of the study, tramadol use in combination with local anesthetic agents for nerve blocks was off label and would have an unknown, yet possible neurotoxic effect on the sciatic nerve in human trial participants with a potential risk outweighing any analgesic benefit.

There seems to exist some potentiation effect of systemically administered tramadol and local anesthesia similar to the systemic effect of dexamethasone on local and regional anesthesia, especially as a part of multimodal analgesia [31,32]. Tramadol has multiple mechanisms of antinociception including activation of μ opioid receptors, inhibition of neuronal reuptake of norepinephrine and serotonin with several metabolites exerting the mentioned effects [29]. Our study shows the potential for tramadol in the setting of combining with regional anesthesia but does not support its block elongating effect after intramuscular administration.

Strengths of our study are the reduced variability of cofounders due to uniform population of patients, operated by one team with identical technique and blocks performed by selected experienced providers with uniform ultrasound guided technique. The use of varying dosage of hyperbaric bupivacaine of 10 to 15 mg for the spinal anesthesia in our trial was unlikely to affect the results, as the spinal block covers a period of up to 4 h from administration of the drug prior to surgery with non-significant differences in the spinal block times as seen in the trial by Axelsson et al. [33]. The 4 h period is a lot shorter than the sciatic blockade and shorter than the times to first analgesia. The delivered drug remains as a 0.5% solution and therefore 10–15 mg is 2–3 mL administered intrathecally, with the dose adjusted to the height of the patient. Adjustment of dose to height is special in spinal anesthesia as most dosing regimens are based on patient weight.

Study shortcomings are the relatively small size, inability to detect effects smaller than assumed that may have been masked by the long duration of the sciatic nerve block itself, a long acquisition period, and also both the bupivacaine used for the nerve block and tramadol dose were not adjusted to patient body weight. Sensory and motor block onset times of the sciatic nerve were not assessed as the spinal blockade masked any possibility of testing, which could have led to a possible missed sciatic nerve block failure.

5. Conclusions

In conclusion, a concomitant intramuscular single dose of 100 mg of tramadol does not extend the duration of the analgesic effect of a sciatic nerve block with 20 mL of 0.25% bupivacaine beyond a clinically relevant postulated 2 h in patients undergoing calcaneal fracture nailing. Our study did not demonstrate statistically relevant longer times to first opioid administration in patients receiving intramuscular tramadol, although such a trend could be seen. An opioid sparing effect could not be demonstrated in our trial. Sciatic nerve blockade for calcaneal fracture nailing may provide in itself a clinically relevant analgesic effect.

Author Contributions: Conceptualization M.J., G.G. and R.K.; Methodology M.J., G.G. and R.K.; Software G.G.; Validation P.W., P.N. and J.T.; Formal analysis M.J. and G.G.; Investigation M.J., G.G. and R.K.; Resources M.J., G.G., R.K. and J.T.; Writing—original draft preparation G.G. and M.J.; Writing—review and editing P.N., J.T. and P.W.; Supervision P.N. and J.T.; project administration M.J. and G.G. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Medical University of Warsaw Bioethical Committee (Approval number KB/128/2017, Chairperson Prof. Zbigniew Wierzbicki) for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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VII. RESULTS AND SUMMARY

The dissertation comprises three original papers centered on the topic of improving regional anesthesia practices in distinct surgical conditions.

In all papers, the role of RA techniques was to optimize the analgesic effect of standard multimodal pain management. The specific goals of overcoming the shortcomings of RA may have been different, but the aims are patient-centered and focused on the most optimal analgesia pathways in niche regions of surgery and anesthesia.

In the first original research paper presented in this thesis, the more optimal fascial plane block was considered. With the outbreak of RA techniques, especially novel forms of blocks such as the fascial plane blocks including the TAP and QLB blocks, we undertook a comparison of these blocks in a special population of patients with end-stage renal failure receiving a kidney transplant. There is extensive debate on which fascial plane block may provide a better analgesic profile following surgery. We constructed the study to optimize the analgesia – the TAP block may have been easier to perform, but it does not have the potential of the added visceral analgesia that could have been seen with the QLB block. The QLB block is more cumbersome and requires additional expertise to perform – however, if the analgesic effect would surpass the TAP block and this may be worth the training in providing the deeper QLB block. Analgesic regimens for the renal transplant recipient are limited and any additional opioid sparing is beneficial. Nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in this patient group, leaving paracetamol and metamizole as sole non-opioid analgetic drugs. Similar debates exist in the choice of the TAP versus QLB including analgesia for cesarean section, inguinal hernia repair, and hysterectomy, [51,52,53]. In the case of our first publication comparing the simpler TAP block to the more robust QLB for renal transplant surgery, we demonstrated a reduction in the cumulative fentanyl in the first 24 hours when QLB was used, but there was no statistical difference in pain scores or incidence of opioid-related side effects making the benefit of QLB over TAP marginal.

In the second original research paper, the straightforward administration of intrathecal morphine (ITM) was compared to a novel femoral triangle block of the femoral nerve branches for analgesia in total knee arthroplasty. The explosive interest in ultrasound-guided regional

anesthesia has created a new controversy – with the wanted sensory block comes a motor block. This can be seen especially in regional blocks for limb surgery. Extending the duration of the peripheral nerve block may actually limit fast and enhanced recovery due to immobility. On the other hand, poor control of postoperative pain is a limiting factor in early postoperative recovery. The number of total knee replacement surgeries is on the rise – in part due to the aging population, but also secondary to the obesity pandemic [54,55]. Early Recovery After Surgery (ERAS) is beneficial in patients that have undergone knee replacement surgery and a shift towards motor sparing blocks is emerging. As total knee arthroplasty (TKA) generates severe postoperative pain, surpassing even extensive hip replacement surgery, abandoning RA blocks may not be the optimal route. RA techniques for knee arthroplasty have evolved from continuous epidural analgesia through a gold standard of femoral nerve block – until recently the most effective and recommended block for knee surgery. However, with the advent of fast and enhanced tracks following TKA – risks related to extensive quadriceps muscle weakness have become an issue. Although not linked directly, traumatic falls during rehabilitation following TKA have pushed recommendations for postoperative analgesia into more distal lower limb blocks to spare at least part of the quadriceps muscle strength [56]. One such block is the femoral triangle block (FTB), which involves injecting local anesthetics in the distal part of the femoral triangle to anesthetize the saphenous nerve and the nerve to vastus medialis: both important in sensory knee innervation. In our study, we demonstrated that the simpler option of administering intrathecal morphine had a similar analgesic effect, but was related to more adverse effects including two cases of respiratory depression, giving a benefit of the femoral triangle block.

In the third original research paper, the role of tramadol as an adjuvant in sciatic nerve block was assessed. The role of adjuvants in regional anesthesia is under current research due to the ease with which personalization of the block characteristics can be modeled by adding a drug to the administered local anesthetic. The present consensus is not to consider tramadol as an adjuvant in regional anesthesia due to conflicting results, but RCTs are limited to select blocks such as the interscalene plexus block with contradictory results [44]. Prior to our trial design, we observed two cases of a beneficial extension of the analgesic effect of a sciatic nerve block for calcaneal fracture fixation. To confirm our finding, we designed an RCT with intramuscular tramadol. The intramuscular route was chosen to avoid administering tramadol

in an off-label perineural dose, but with a possibly similar pharmacokinetic resemblance to such a mode of administration, and also to replicate the two above mentioned cases. It should be noted that the intramuscular injection remained painless as it was administered after the onset of spinal anesthesia in the contralateral non-operated thigh. The trial helped to prove that sciatic nerve block has an optimal analgesic effect on itself, and we could not demonstrate the extension of the analgesia by systemic tramadol in conjunction with the block. The study might have been underpowered to report an opioid-sparing effect, but a visible trend was seen.

Multiple options and techniques of regional anesthetic blocks are possible for a given procedure, but the balance between the benefit and shortcomings is under constant debate, requiring well-structured research studies in the form of RCTs for the creation of recommendations such as the PROcedure SPEcific postoperative pain managemenT (PROSPECT) guides and national or international pain management guidelines.

Conclusions:

- Regional anesthesia has a major role in multimodal analgesia for differing types of surgeries ranging from renal transplantation to pain-generating orthopedic procedures.
- Different approaches to modifying regional anesthetic blocks may be made with a focus on procedure-specific points:
    - A Quadratus Lumborum Block type II being marginally more optimal in opioid sparing than the Transversus Abdominis Plane block for renal transplantation,
    - The Femoral Triangle Block being a possibly safer, but equipotent analgesic modality to intrathecal morphine,
    - Tramadol as an adjuvant did not show any major benefit over a standard sciatic nerve block for calcaneal intramedullary fracture fixation.

In the search for the most optimal routes in multimodal analgesia and to find a balance between the benefits and risks related to specific regional blocks, we have added three RCTs to the bulk of knowledge.

VIII. BIBLIOGRAPHY

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IX. BIOETHICAL COMMITTEE APPROVALS OF STUDIES CONSTITUTING THE DISSERTATION

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

KB/..68../2016

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym

w dniu 15 marca 2016 r. po zapoznaniu się z wnioskiem:

dr n. med. Marcin Kołacz
I Klinika Anestezjologii i Intensywnej Terapii,
ul. Lindleya 4, 02-005 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt.: **„Porównanie skuteczności blokad przestrzeni międzypowięziowych w obrębie przedniej i bocznej ściany brzucha wykonywanych pod kontrolą USG w analgezji okołooperacyjnego u pacjentów poddanych przeszczepieniu nerki. Badanie kliniczne, randomizowane, wieloośrodkowe",**

wyraża następującą

o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .
W załączeniu: skład komisji oraz lista obecności

Przewodniczący Komisji Bioetycznej

Prof. dr hab. n. med. Zbigniew Wierzbicki

*niepotrzebne skreślić

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

KB/.107./2016

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym

w dniu 10 maja 2016 r. po zapoznaniu się z wnioskiem:

dr hab. n. med. Janusz Trzebicki
I Klinika Anestezjologii i Intensywnej Terapii ,
ul. Lindleya 4, 02-005 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt. **„Ocena bólu pooperacyjnego u pacjentów po protezoplastyce stawu kolanowego"**

wyraża następującą
opinię

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .
W załączeniu: skład komisji oraz lista obecności

Przewodniczący Komisji Bioetycznej

Prof. dr hab. n. med. Zbigniew Wierzbicki

*niepotrzebne skreślić

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

KB/...128.../2017

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 06 czerwca 2017r. po zapoznaniu się z wnioskiem:

Dr hab. n. med. Janusz Trzebicki
I Klinika Anestezjologii i Intensywnej Terapii ,
ul. Lindleya 4, 02-005 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt. : „Ocena wpływu jednoczasowego podania tramadolu z blokiem nerwu kulszowego na wydłużenie czasu utrzymywania się skutecznej blokady czuciowej u pacjentów operowanych z powodu złamania kości stopy.

wyraża następującą
o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .
W załączeniu: skład komisji oraz lista obecności

Przewodniczący Komisji Bioetycznej

Prof. dr hab. n. med. Zbigniew Wierzbicki

*niepotrzebne skreślić

X. MANUSCRIPT CO-AUTHOR DECLARATIONS

Warszawa, 16.03.2023
(miejscowość, data)

Dr n. med. Marcin Kołacz
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation. A randomised trial. *Eur J Anaesthesiol* 2020; 37:773–779** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *koncepcja i projekt badania, czynny udział w badaniu, zebranie danych, analiza i interpretacja wyników, krytyczna ocena, napisanie artykułu.*
Mój udział procentowy w przygotowaniu publikacji określam jako 25 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 25 % (autor korespondencyjny),

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Olsztyn, 10.02.2023
(miejscowość, data)

MARCIN MIESZKOWSKI
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy dwuośrodkowej pt. **Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation. A randomised trial. *Eur J Anaesthesiol* 2020; 37:773–779** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *koncepcja i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, krytyczna ocena, ostateczna akceptacja wersji publikacji do druku.*

Mój udział procentowy w przygotowaniu publikacji określam jako 25 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka,
(imię i nazwisko kandydata do stopnia)

dr n. med. Marcin Mieszkowski
specjalista anestezjologii
i intensywnej terapii, DESAIC
2593727

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Krzysztof Zagórski
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation. A randomised trial. *Eur J Anaesthesiol* 2020; 37:773–779** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *czynny udział w badaniu, zebranie danych, analiza i interpretacja wyników, krytyczna ocena.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład Marka Janiaka w powstawanie publikacji określam jako 25 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

Krzysztof Zagórski
.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Beata Byszewska
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation. A randomised trial. *Eur J Anaesthesiol* 2020; 37:773–779** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *czynny udział w badaniu, zebranie danych, analiza i interpretacja wyników.*

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(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

Beata Byszewska
.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Olsztyn, 10.02.2023
(miejscowość, data)

MAŁGORZATA WERYK-DYŚKO
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy dwuośrodkowej pt. **Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation. A randomised trial.** ***Eur J Anaesthesiol*** **2020; 37:773–779** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *czynny udział w badaniu, zebranie danych, analiza i interpretacja wyników, krytyczna ocena, ostateczna akceptacja wersji publikacji do druku.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka,
(imię i nazwisko kandydata do stopnia)

lek. Małgorzata Weryk
specjalista pielęgniarstwa
anestezjologii i intensywnej terapii
29600

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Olsztyn, 10.02.2023
(miejscowość, data)

DARIUSZ ONICHIMOWSKI
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy dwuośrodkowej pt. **Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation. A randomised trial. *Eur J Anaesthesiol* 2020; 37:773–779** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *koncepcja badania, analiza i interpretacja wyników, krytyczna ocena, ostateczna akceptacja wersji publikacji do druku, nadzór merytoryczny.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 25 %,
(imię i nazwisko kandydata do stopnia)
obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka,
(imię i nazwisko kandydata do stopnia)

dr hab. n. med.
Dariusz Onichimowski
Specjalista Anestezjologii i Intensywnej Terapii
1530458

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Rafał Kowalczyk
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Efficacy and Side Effect Profile of Intrathecal Morphine versus Distal Femoral Triangle Nerve Block for Analgesia Following Total Knee Arthroplasty: A Randomized Trial.** ***Journal of Clinical Medicine*** **2022; 11:6945** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *koncepcja i projekt badania, czynny udział w badaniu, zebranie danych, analiza i interpretacja wyników.*
Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Grzegorz Górniewski
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Efficacy and Side Effect Profile of Intrathecal Morphine versus Distal Femoral Triangle Nerve Block for Analgesia Following Total Knee Arthroplasty: A Randomized Trial.** ***Journal of Clinical Medicine*** **2022; 11:6945** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *koncepcja i projekt badania, czynny udział w badaniu, zebranie danych, napisanie artykułu, analiza i interpretacja wyników.*

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obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Kinga Olczyk-Miiller
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Efficacy and Side Effect Profile of Intrathecal Morphine versus Distal Femoral Triangle Nerve Block for Analgesia Following Total Knee Arthroplasty: A Randomized Trial.** ***Journal of Clinical Medicine*** **2022; 11:6945** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *koncepcja i projekt badania, zebranie danych..*
Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Marcin Kowalski
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Efficacy and Side Effect Profile of Intrathecal Morphine versus Distal Femoral Triangle Nerve Block for Analgesia Following Total Knee Arthroplasty: A Randomized Trial.** ***Journal of Clinical Medicine*** **2022; 11:6945** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *udział czynny w badaniu.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

Dr. n. med. MARCIN KOWALSKI
ortopeda-traumatolog
ZUS 4171196 REF 9807-67304

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Piotr Nowakowski
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Efficacy and Side Effect Profile of Intrathecal Morphine versus Distal Femoral Triangle Nerve Block for Analgesia Following Total Knee Arthroplasty: A Randomized Trial.** ***Journal of Clinical Medicine*** **2022; 11:6945** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *nadzór merytoryczny, krytyczna ocena.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Dr n. med. Grzegorz Górniewski
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Effect of Intramuscular Tramadol on the Duration of Clinically Relevant Sciatic Nerve Blockade in Patients Undergoing Calcaneal Fracture Fixation: A Randomized Controlled Trial. *Healthcare* 2023, 11, 498** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *koncepcja i projekt badania, zebranie danych, czynny udział w badaniu, napisanie artykułu.*
Mój udział procentowy w przygotowaniu publikacji określam jako 10 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Dr n. med. Rafał Kowalczyk
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Effect of Intramuscular Tramadol on the Duration of Clinically Relevant Sciatic Nerve Blockade in Patients Undergoing Calcaneal Fracture Fixation: A Randomized Controlled Trial.** ***Healthcare*** **2023, 11, 498** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *koncepcja i projekt badania, zebranie danych, czynny udział w badaniu, akceptacja wersji do druku.*
Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Dr n. med. Piotr Wasilewski
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Effect of Intramuscular Tramadol on the Duration of Clinically Relevant Sciatic Nerve Blockade in Patients Undergoing Calcaneal Fracture Fixation: A Randomized Controlled Trial. *Healthcare* 2023, 11, 498** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *krytyczna ocena, akceptacja wersji do druku.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Dr n. med. Piotr Nowakowski
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Effect of Intramuscular Tramadol on the Duration of Clinically Relevant Sciatic Nerve Blockade in Patients Undergoing Calcaneal Fracture Fixation: A Randomized Controlled Trial. *Healthcare* 2023, 11, 498** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *nadzór merytoryczny, krytyczna ocena, akceptacja wersji do druku.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Dr hab. n. med. Janusz Trzebicki
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Transversus abdominis plane block versus quadratus lumborum block type 2 for analgesia in renal transplantation. A randomised trial. *Eur J Anaesthesiol* 2020; 37:773–779** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *czynny udział w badaniu, zebranie danych, analiza i interpretacja wyników, krytyczna ocena, nadzór merytoryczny.*
Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Marka Janiaka w powstawanie publikacji określam jako 25 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Dr hab. n. med. Janusz Trzebicki
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Efficacy and Side Effect Profile of Intrathecal Morphine versus Distal Femoral Triangle Nerve Block for Analgesia Following Total Knee Arthroplasty: A Randomized Trial.** ***Journal of Clinical Medicine*** **2022; 11:6945** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *nadzór merytoryczny, krytyczna ocena, akceptacja wersji do druku.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład Marka Janiaka w powstawanie publikacji określam jako 70 %,

obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 01.03.2023
(miejscowość, data)

Dr hab. n. med. Janusz Trzebicki
.....
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Effect of Intramuscular Tramadol on the Duration of Clinically Relevant Sciatic Nerve Blockade in Patients Undergoing Calcaneal Fracture Fixation: A Randomized Controlled Trial.** ***Healthcare*** **2023, 11, 498** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: *nadzór merytoryczny, krytyczna ocena, akceptacja wersji do druku.*

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

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obejmował on: *koncepcję i projekt badania, zebranie danych, czynny udział w badaniu, analiza i interpretacja wyników, napisanie artykułu, krytyczna ocena, akceptacja wersji do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Marka Janiaka

(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników