Strategies for the management of postoperative pain in total knee arthroplasty: integrative review

Estratégias para o manejo da dor pós-operatória em artroplastia total de joelho: revisão integrativa

Márcia Carla Morete-Pinto[1], Arthur Fogel Sousa-Correa[1]

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ABSTRACT

BACKGROUND AND OBJECTIVES: Total knee arthroplasty is one of the most common surgeries performed on patients with osteoarthritis or rheumatic arthritis of the knee. However, total knee arthroplasty is associated with moderate to severe pain after the operation. In orthopedics, the prevalence of chronic pain after total knee arthroplasty is much higher than after total hip arthroplasty. The aim of this study was to analyze the current knowledge about postoperative pain in knee arthroplasty.

CONTENTS: An integrative review of clinical trials published in English and Portuguese was carried out in the Scielo, Pubmed and LILACS databases. The inclusion criteria consisted of articles published in the last five years, available in full, that addressed the proposed theme. Editorials, letters to the editor, dissertations, repeated articles that did not correspond to the theme were excluded. The search and selection process of the studies followed the PRISMA recommendations. Of the 155 articles found, 58 articles were selected for the present study following the above-mentioned recommendations.

CONCLUSION: Several classes of local and systemic drugs, including non-steroidal anti-inflammatory drugs, opioids, and local anesthetics have been used to fight the nociceptive component of postoperative pain. Furthermore, early rehabilitation contributes to better quality of life, self-esteem and reduce the time of hospitalization and hospital expenses.

Keywords: Arthroplasty, Knee, Pain, Postoperative pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A artroplastia total do joelho é uma das cirurgias mais comuns realizadas em pacientes com osteoartrite ou artrite reumatoide do joelho. No entanto, a artroplastia total do joelho está associada a dor moderada a intensa no pós-operatório. Na ortopedia, a prevalência de dor crônica após a artroplastia total do joelho é muito maior do que após a artroplastia total do quadril. O objetivo deste estudo foi analisar as evidências científicas sobre o manejo da dor no pós-operatório de artroplastia de joelho.

CONTEÚDO: Foi realizada uma revisão integrativa nas bases de dados Scielo, Pubmed e LILACS de ensaios clínicos nos idiomas inglês e português. Os critérios de inclusão consistiram em artigos publicados nos últimos cinco anos, disponíveis na íntegra, que abordassem a temática proposta. Excluíram-se editoriais, cartas ao editor, dissertações, artigos repetidos e que não correspondessem à temática. O processo de busca e seleção dos estudos seguiu as recomendações PRISMA. Dos 155 artigos encontrados, 58 artigos foram selecionados para o presente estudo seguindo as recomendações citadas.

CONCLUSÃO: Várias classes de fármacos locais e sistêmicos, incluindo anti-inflamatórios não esteroides, opioides e anestésicos locais, têm sido utilizadas para combater o componente nociceptivo da dor pós-operatória. Além disso, a reabilitação precoce contribui para a melhora na qualidade de vida, autoestima e reduz o tempo de internação e os custos hospitalares.

Descritores: Artroplastia, Dor, Dor pós-operatória, Joelho.

INTRODUCTION

Total knee arthroplasty (TKA) has been identified as one of the most effective surgeries for knee arthritis[1,2]. TKA is one of the most common elective surgical procedures done in elderly patients to treat pain and functional limitation due to refractory knee arthritis[3] and is associated with optimal arthritis pain relief in the majority of these patients. However, many patients experience moderate to severe pain during the immediate postoperative period because the surgery involves extensive bone resection[2,4,5]. In the United States, 8 to 15% of patients submitted to TKA have moderate to severe residual joint pain persisting for 2 to 5 years after the procedure[6,7]. Postoperative pain (POP) is most often underestimated and undertreated[2-4], resulting in distress and low patient satisfaction, also associated with longer hospital stays, resistance to rehabilitation exercises, poorer health-related quality of life, and increased morbidity related to complications[8,9].

Márcia Carla Morete-Pinto – https://orcid.org/0000-0001-7641-9957;
Arthur Fogel Sousa-Correa – https://orcid.org/0000-0001-9816-0616.

1. Albert Einstein Israeli Institute for Education and Research, Pain Service, São Paulo, SP, Brazil.

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Correspondence to:
Arthur Fogel Sousa-Correa
Rua Conselheiro Brotero, 906 – Bairro Santa Cecília
01232–010 São Paulo, SP, Brasil.
E-mail: arthurfscorrea@gmail.com

At the present time, no gold-standard[10] protocol for the reduction of pain intensity without increasing nausea and vomit was identified. Previous studies have reported that postoperative serum levels of interleukin-6 (IL-6) cytokine and C-reactive protein (CRP) may be high[11,12]. Steroids may be associated with reduced levels of IL-6 and CRP and thus relieve pain associated with various procedures[1].

Several studies have compared the efficacy of adjuvant steroids as a component of multimodal anesthesia after TKA. However, previous results must be interpreted with caution due to the lack of robustness and homogeneity among these studies[1]. Long-term unfavorable pain outcomes have been observed in 10 to 34% of patients after TKA[13].

Studies that have assessed pain and its postoperative consequences in the medium and long term are scarce. Studies to date have not comprehensively examined the post-TKA pain experience or evaluated the presence of discrete subgroups of individuals with different pain patterns at 6 to 12 months after TKA. This factor is an important knowledge gap, given (1) the co-occurrence of POP during post-TKA physical rehabilitation[14,15]; (2) the treatment of early POP with opioids[16,17] and the indiscriminate use of opioids[18,19]; and (3) the significant prevalence of persistent pain after TKA[6-13].

If early patterns of pain can be used to identify patients likely to have prolonged pain, clinical treatment options can be developed and adapted to change this outcome. Emerging tools for trajectory analysis that have been shown to be associated with different patterns of care and health care costs[20] offer new insights into patients pain experience and outcomes after TKA.

Authors[21] have reported that pain occurring after TKA is more painful than in any other orthopedic surgery, including total hip arthroplasty. The mechanism of POP involves sensitization of peripheral nociceptive nerve terminals and central neurons[22]. Recently, sensitization of central neurons has been shown to be more important than peripheral nerve sensitization[23,24].

Moderate or severe pain after TKA delays recovery and rehabilitation. POP is a mixed pain model, with nociceptive and neuropathic components. This pain leads to local inflammatory response, nociceptor stimulation and nociceptive pain. Surgical stimulation also leads to sensitization of the neurons, which is associated with increased pain[24,25]. This is called central sensitization (CS).

CS may be temporary or permanent, depending on the neuronal phenotypic alterations, and is an important phenomenon because it helps in the understanding of chronic or amplified pain. CS occurs after intense or repetitive stimulation of the nociceptor present in the periphery, inducing a reversible increase in excitability and synaptic efficacy of the neurons of the central nociceptive pathway[26]. The sensitivity induced in the nociceptor of the somatosensory system is adaptive, making the system hyperalert in conditions where there is a greater risk of new injury, such as immediately after exposure to intense or noxious stimuli. Several classes of drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthetics have been used to fight the nociceptive component of POP[27,28].

The objective of the updated POP therapy is to increase pain relief and decrease opioid consumption by combining drugs and analgesic techniques to reduce opioid-related complications. Several modalities are employed to reduce POP after TKA. One study, for instance, investigated pregabalin, indicated for neuropathic pain, and ondansetron, a drug that interrupts descending serotoninergic processing in the central nervous system, on spinal neuronal hyperexcitability and visceral hypersensitivity in a rat model of opioid-induced hyperalgesia. The researchers observed that the inhibitory action of pregabalin in animals with opioid-induced hyperalgesia is neither dependent on neuropathy nor dependent on the positive regulation of the voltage-dependent calcium channel subunit, proposed mechanisms essential for the efficacy of pregabalin in neuropathy, concluding that pregabalin reduces spinal neuronal hyperexcitability in morphine-treated animals[28].

Another study illustrated the central impact of neuropathy, leading to an imbalance in descending excitations and inhibitions, where underlying noradrenergic mechanisms explain the relationship between conditioned pain modulation and tapentadol and duloxetine use in patients, suggesting that pharmacological strategies through the manipulation of the monoamine system can be used to increase diffuse noxious inhibitory control (DNIC) in patients by blocking descending facilities with ondansetron or increasing norepinephrine inhibitions, possibly reducing chronic pain[29]. The use of opioids is restricted due to adverse effects such as nausea, vomiting, and pruritus[30].

The objective of the present study was to perform an analysis on the current knowledge about POP in TKA.

CONTENTS

Literature integrative review that methodically, orderly and comprehensively summarizes the results obtained in research on a specific topic. Thus, the reviewer/researcher can elaborate an integrative review with distinct goals, directing it to the definition of concepts, theory review or methodological analysis of research included within a determined subject[31].

Based on the above, the present work opted for the integrative review based on the Whittemore and Knafl[32] referential, revised by Hopia, Latvala e Liimatainen[33], in order to answer the following guiding question: ''what is the current knowledge of studies about POP in TKA"?

The search was conducted in Pubmed, LILACS and Scielo databases in the months of January and February 2020. The search strategy started with the selection of Health Science Descriptors (DeCS) pertinent to the guiding question. The search in Pubmed used the Medical Subject Headings (MeSH) and the Boolean operator AND to cross-reference the descriptors "pain", "postoperative pain" and "knee arthroplasty", in English and Portuguese, as follows: "X AND Y".

The inclusion criteria consisted of articles published in the last five years, available in full, in English and Portuguese, and that addressed the proposed subject. Editorials, letters to the editor, dissertations, duplicate articles, and those which did not correspond to the theme were excluded.

The search and selection process followed the PRISMA[34] recommendations as shown in figure 1.

Included studies should have been clinical trials on humans published in the last five years in Portuguese and English. For data collection, an instrument was constructed containing the following variables: authors; study objective(s); methodological approach;

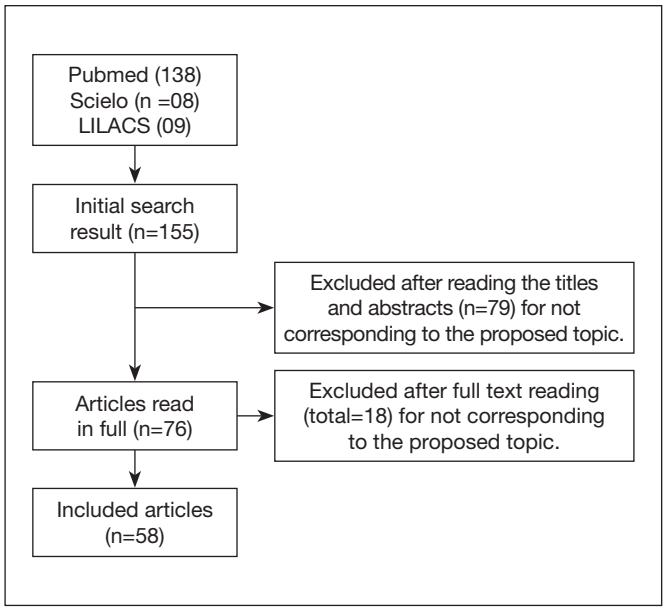

Figure 1. PRISMA flowchart of data on knee arthroplasty postoperative pain. São Paulo, 2020

type of study; sample (size, recruitment, characteristics, inclusion and/or exclusion criteria); statistical analysis (statistical treatment); results; conclusions; implications for clinical practice; assessment of methodological rigor; and identification of limitations or biases. Of the 155 preselected articles, 97 were excluded (for not corresponding to the proposed topic).

Of the 58 that compose the sample, all are in the English language. The studies were represented by 22 countries of origin, being: Taiwan (n=1/0.6%), Iceland (n=1/0.6%), Spain (n=1/0.6%), Bosnia (n=1/0.6%), Switzerland (n=1/0.6 %), Denmark (n=1/0.6%), Poland (n=1/0.6%), Argentina (n=1/0.6%), India (n=1/0.6%), Brazil (n=2/1.2%), Australia (n=2/ 1.2%), Sweden (n=2/ 1.2%), Netherlands (n=2/1.2%), Italy (n=2/1.2%), Thailand (n=3/1.8%), Japan (n=3/1.8%), Korea (n=4/1.8%), UK (n=4/2.4%), Turkey (n=5/3%), USA (n=11/6.8%), China (n=10/6%).

As for language, the studies are in English (94%) and Portuguese (6%). Regarding the type of study, all are clinical trials.

As for the year of publication, 8 are from 2015, 9 from 2016, 9 from 2017, 19 from 2018 and 13 from 2019, showing that they are relatively current research and, like any study, they have limitations, biases, and disagreements with each other.

Table 1. Synthesis of assessed studies, in chronological order, their methodological differences and conclusions. São Paulo, Brazil, 2020.

Authors	Sample	Methodology	Conclusion
Li et al.[37]	60 patients	Randomized clinical Trial	The femoral nerve and the sciatic nerve block applied to the TKA may inhibit the tourniquet reaction, maintaining the hemodynamic stability, reducing the anesthetic dosage and reducing POP.
Shen et al.[67]	36 patients	Randomized, double-blind study	Intra-articular bupivacaine in combination with intravenous parecoxib may improve pain relief and reduce the demand for rescue analgesics in patients undergoing TKA.
YaDeau et al.[64]	120 patients	Prospective, randomized, blinded, controlled study	Pregabalin increased sedation but did not increase patient satisfaction. This study did not support routine perioperative pregabalin for patients with TKA.
Olive et al.[65]	81 patients	Randomized clinical trial	In patients without CFNB, the use of SMI was blinded. 81 patients were randomized. At 24 hours, the SMI-only group reported more pain than the other groups. At 18 to 24 hours, the SMI group used more morphine than other groups. Patients who received SMI had pruritus. There were no significant differences regarding nausea and sedation by SpO_2. This study showed that a CFNB resulted in reduced pain, lower morphine consumption and better mobilization in 24h compared to SMI. This study showed no statistically significant differences between CFNB alone and CFNB + SMI.
Sarridou et al.[66]	90 patients	Randomized clinical trial	Intravenous parecoxib in association with the continuous femoral block provided a superior analgesic efficacy and opioid-sparing effects in patients undergoing TKA.
Wylde et al. [72]	300 patients	Randomized clinical trial	Local anesthetic infiltration reduces chronic pain by up to one year, suggesting that routine use of infiltration could improve long-term pain relief.
Frassanito et al.[89]	40 patients	Randomized clinical trial	Preoperative intravenous administration of Mg did not influence postoperative pain control and analgesic consumption after TKA.
Ali et al.[41]	200 patients	Double-blind, randomized study	CIAA had no clinically relevant effect on POP and length of hospital stay. More infections were found in the therapy group and, therefore, the use of CIAA was discontinued.
Tonelli Filho[55]	21 patients	Prospective clinical trial	The lateral via provided better postoperative lateral patellar tilt in valgus knee arthroplasties.
Shin et al.[90]	44 patients	Randomized clinical trial	Magnesium sulfate administration significantly reduced POP and minimized the difference in pain intensity between the first and second operations.
Yun et al.[57]	45 patients	Randomized clinical trial	The results indicate that intravenous perioperative administration of dexmedetomidine decreases postoperative serum IL-6 levels and an optimal analgesic effect.

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Table 1. Synthesis of assessed studies, in chronological order, their methodological differences and conclusions. São Paulo, Brazil, 2020 – continuation

Authors	Sample	Methodology	Conclusion
Heo et al.[77]	82 patients	Double-blind, randomized, prospective study	Additional fentanyl showed no prominent increase in analgesic effect in the CFNB field after TKA.
Jianda et al.[58]	75 patients	Randomized clinical trial	Preemptive analgesia added to a multimodal analgesic regimen improved analgesia, reduced inflammatory reaction, and accelerated functional recovery in the first postoperative week, but didn't improve long-term function.
Gupta et al.[78]	78 patients	Randomized clinical trial	Ibuprofen IV combined with acetaminophen IV showed additional benefit in terms of improved pain scores only on postoperative day 3, fewer potential adverse events related to opioid use, and less opioid use when compared to ibuprofen IV alone.
Sundarathiti et al.[80]	68 patients	Randomized clinical trial	Although in some patients CFNB is inadequate, a mini dose of subarachnoid morphine (0.035mg) in addition to CFNB has shown to be effective with minimal adverse effects.
Blikman et al. [50]	59 patients	Prospective, multicentric, randomized study	The knowledge gained from this study can potentially improve pain relief and postoperative rehabilitation after TKA. Furthermore, due to an extensive preoperative treatment period, it could provide specific information on the efficacy of duloxetine in patients with advanced hip and knee osteoarthritis with possible NP/CS.
Tsukada et al.[63]	77 patients, 67 women and ten men	Double-blind, randomized clinical trial	The addition of corticosteroids to the periarticular injection significantly decreased premature POP. Further studies are needed to confirm the safety of corticosteroid in periarticular injection.
Wall et al.[42]	269 patients	Randomized clinical trial	Periarticular infiltration is a viable and safe alternative to FNB for immediate POP relief after TKA.
Gudmundsdottir et al.[76]	69 patients	Randomized clinical trial	The results indicated that there is no benefit of continuous infusion of ACB added to a single dose of LIA compared to LIA alone on pain. In addition, ACB showed no superiority in the ability to ambulate at 2 days after the operation.
Ortiz-Gómez et al.[44]	639 patients	Randomized, prospective, clinical study	Peripheral nerve blocks with perineural dexamethasone improve postoperative analgesia of TKA. The addition of dexamethasone to ACB opens new possibilities for improving analgesia of TKA and should be investigated as an alternative to femoral nerve block.
Álvarez et al.[38]	39 patients	Randomized clinical trial	CFNB combined with sciatic nerve block provides efficacy in postoperative analgesia in patients undergoing TKA, with lower pain scores after 24 h and lower incidence of adverse effects and bleeding compared to subarachnoid morphine.
Canakci, Unal and Guzel[83]	60 patients	Randomized clinical trial	The technique of SPC blockade with bupivacaine hydrochloride ensured greater hemodynamic efficiency in the perioperative in elderly high-risk patients undergoing TKA.
Deng et al. [68]	100 patients	Double-blind, randomized, controlled study	Compared to postoperative analgesia of CFNB alone, CFNB with PALI can relieve pain at rest and pain during passive motion after TKA. CFNB with PALI may shorten the time to perform an active straight leg raise and the capacity time to achieve 90° knee flexion. Thus, some patients could improve postoperative rehabilitation training.
Barrington et al.[82]	119 patients	Multicentric, controlled, randomized, prospective study.	This study showed potential pain control at 6 and 12 h in the LB and subarachnoid morphine groups compared to the ropivacaine group, at the expense of much higher incidences of pruritus (itching) in the subarachnoid morphine group. Based on these results, the use of PAI with LB was preferred as an alternative to spinal anesthesia with subarachnoid morphine as a result of similar control of POP and the potential for reduced adverse events.
Jahic et al.[59]	20 patients	Prospective study	The study proved statistically significant difference between the KS and FS between the intervention and control group at test time: immediately before surgery – meaning that the KS and FS Test increased after the pre-rehabilitation program (6-week home exercise program). The knee score was significantly different between the two groups observed postoperatively, 3 and 6 months, while the FS was not significantly different in that period. Preoperative home exercises provide better preoperative KS and FS and better KS up to 6 months postoperatively. However, 12 months postoperatively, there was no significant difference between the intervention and control group for the KS and FS.
Bugada et al.[62]	563 patients	Prospective, observational, multicenter study.	Continuous regional anesthesia provides analgesic benefit for up to one month after surgery but did not influence PPOP at 6 months. Better pain control at one month was associated with reduced PPOP. Patients with higher expectations regarding the surgery, higher baseline inflammation, and a pessimistic outlook are more likely to develop PPOP.

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Table 1. Synthesis of assessed studies, in chronological order, their methodological differences and conclusions. São Paulo, Brazil, 2020 – continuation

Authors	Sample	Methodology	Conclusion
Liu et al.[35]	226 patients	Randomized clinical trial	The preoperative analgesia group also exhibited decreased GPA scores compared to the postoperative analgesia group at 2, 6, 12, 24 and 48 h after surgery. Most interestingly, patients in the preoperative analgesia group consumed less GPA compared to patients in the postoperative analgesia group 72 h after the operation. No difference in incidence of adverse events was observed between the two groups.
O'Neal et al.[79]	174 patients	Single-center, randomized, double-blind, placebo-controlled clinical trial	Neither intravenous nor oral acetaminophen provided additional analgesia in the immediate postoperative period when administered as adjunct multimodal analgesia in patients undergoing TKA in the context of spinal anesthesia.
Novello-Siegenthaler et al.[52]	80 patients	Prospective, randomized clinical trial	In this study, the catheter port configuration did not influence the efficacy of CFNB. In this scenario: the quality of analgesia was similar, without reduction in local anesthetic or morphine consumption and equivalent postoperative quadriceps weakness.
Sztain et al.[45]	50 patients	Randomized clinical trial	For CACB accompanied by intraoperative periarticular local anesthetic infiltration, analgesia the day after TKA is improved with a catheter inserted at the midpoint level between the anterior superior iliac spine and the superior border of the patella compared to a more distal insertion closer to the adductor hiatus.
Wu, Lu and Ma[74]	50 patients	Randomized clinical trial	The administration of 10mg dexamethasone 1h before surgery and repeated at 6h postoperatively can significantly reduce the postoperative CRP and IL-6 level and the incidence of PONV, relieve pain, achieve an additional analgesic effect and improve early ROM compared to the other two groups in TKA.
Tan et al.[75]	200 patients	Randomized clinical trial	MBA does not relieve lateral knee pain in the early stage, but provides similar analgesic effect and better early rehabilitation efficacy compared to FNB in patients undergoing TKA.
Bian et al.[69]	88 patients	Randomized clinical trial	In preemptive multimodal analgesia strategies, parecoxib sodium can significantly decrease the VAS score in the short term, relieve pain immediately after surgery, and does not increase the incidence of complications. Parecoxib sodium is a safe and effective drug for the perioperative analgesic treatment of TKA.
Shi et al.[70]	110 patients with ages between 30 and 85 years	Prospective, randomized clinical trial	Intraoperative periarticular injection with multimodal drugs significantly relieved pain after surgery and reduced the requirement for NSAIDs. This injection also improved patient satisfaction and joint ROM without apparent risks after TKA.
Fransen et al.[60]	50 patients	Controlled randomized clinical trial	The fast-track protocol for primary TKA presented significantly lower knee pain scores and improved functional outcome in the first 7 days after TKA compared to a regular protocol.
Erkılıç et al.[86]	52 patients	Randomized clinical trial	Although preemptive oral gabapentin administration didn't reduce postoperative pain and analgesic needs during surgery, it attenuated IL-6 production on the first postoperative day.
Sargant et al.[47]	86 patients	Prospective, randomized study	CACB extended to five days provided superior analgesia and improved quality of recovery postoperatively on days four and five compared to a three-day infusion. This benefit didn't extend beyond the infusion period. No statistically significant differences between groups were identified for other secondary outcome measures
Zlotnicki et al.[84]	80 individuals	Prospective, randomized study	No significant improvements were observed between the LB and plain bupivacaine injection groups in overall pain reduction, ROM, or total drug use. At 24h, small statistically significant differences in physical therapy pain scores were observed in patients with LB vs plain bupivacaine and control, but these differences didn't persist at long term. Both preparations demonstrated statistically significant improvements in ROM when compared to historical controls, but no differences were observed between preparations. In general, minimal significant differences were observed between LB and plain bupivacaine at early and late time points. Both preparations of the periarticular injection demonstrated superiority over pain control regimens but were relatively equivalent to each other in direct comparison.

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Table 1. Synthesis of assessed studies, in chronological order, their methodological differences and conclusions. São Paulo, Brazil, 2020 – continuation

Authors	Sample	Methodology	Conclusion
Kaczocha et al.[24]	42 patients	Double-blind, prospective, randomized study	Subarachnoid morphine administration reduced POP 4 h after TKA surgery compared with placebo and reduced postoperative systemic opioid consumption. At baseline, subarachnoid morphine led to a significant reduction in AEA, 2-AG, and OEA levels, but didn't affect PEA or cortisol levels. In patients who received subarachnoid placebo, 2-AG levels were high 4h after surgery, while patients who received subarachnoid morphine presented reductions in AEA, PEA, and OEA when compared to placebo. At 4h after TKA surgery, cortisol levels were significantly high in the placebo group and reduced in those receiving morphine. These results indicated that subarachnoid morphine reduces POP in patients with TKA. Moreover, activation of central opioid receptors negatively modulates endocannabinoid tone, suggesting that potent analgesics may reduce the stimulus for peripheral endocannabinoid production. This study is the first to document the existence of fast communication between the central opioid and peripheral endocannabinoid systems in humans.
Koo et al.[36]	60 patients	Blind, parallel, prospective, randomized clinical study	Analgesia in the two-week therapy group was effective until the third evaluation, while in the other group it was effective only until the second evaluation. The improvement in ROM in the two-week group was also maintained up to the third evaluation.
Manassero et al.[92]	20 patients	Double-blind, prospective, randomized study	This study showed that in the immediate postoperative period after TKA, patients who received oral extended-release COOXN had the same better pain control as those who received IVPCA morphine, with a similar degree of PONV.
Kanadli et al.[39]	100 patients	Prospective, randomized study	The VAS level at 24 h was significantly lower in Group I compared to Group II. Analgesic consumption between zero and 30 minutes was lower in Group II than in Group I; however, it was significantly lower at 6-24 hours in Group I compared to Group II. The qor-40 score was significantly higher in Group I than in Group II. FNB provided more potent analgesia in the first six hours after operation. After 6 h, IFCB demonstrated better pain control. The quality of postoperative recovery was higher in patients with IFCB.
Jaeger et al.[48]	107 patients	Controlled, double-blind, randomized study	Changing the mode of administration of an ACB from continuous infusion to repeated intermittent boluses didn't decrease opioid consumption, pain, nor mobility.
Mont et al.[71]	139 patients	Controlled, double-blind, randomized study	LIA with LB 266 mg plus bupivacaine hcl significantly reduced opioid use and intensity of pain. These findings support the use of LIA with LB for TKA when early discharge is the objective.
Hutchins et al.[85]	140 patients	Single-arm, open, multicentric study	SST 30µg was effective and well tolerated in the treatment of acute moderate to severe POP.
Ilfeld et al.[53]	7 patients	Prospective clinical trial	Percutaneous ultrasound-guided SNP is feasible in the immediate perioperative period and can provide analgesia without the undesirable systemic effects of opioids or quadriceps weakness induced by local anesthetic-based peripheral nerve blocks.
Alexandersson et al.[54]	81 patients	Randomized clinical trial	The hypothesis that rehabilitation-related outcomes would be improved without a tourniquet is not supported by the results. When the results of the study for surgery performed with and without a tourniquet are compared, no clear benefit was observed for either procedure, as the greater amount of pain exhibited by the non-tourniquet group was only evident for a short time and the improved mobility in this group was not observed at a clinically relevant level.
Canbek et al.[46]	123 patients	Randomized clinical trial	The study verified that pain control after TKA was better in those patients treated with CACB compared to those treated with single-dose ACB. Patients treated with CACB also had better ambulation and functional recovery after TKA.
Borys et al.[40]	85 patients	Randomized clinical trial	FNB was associated with less intense perception of pain after TKA. However, ACB was associated with anterior mobility rehabilitation.
Iglesias et al.[61]	42 patients	Prospective, randomized clinical trial	The continuous infusion pump of analgesia, compared to the formal intermittent intravenous regimen, presented better pain control, decreasing the patient's perception of pain, improving tolerance to physical therapy, and reducing, on average, 15h of hospitalization and, therefore, the costs of surgery.
Matthews et al.[91]	57 patients with ages between 40 and 83 years	Prospective, randomized study	The application of a compression dressing after TKA did not result in any clinical improvement in limb circumference, ROM, or pain. Based on this study, the belief is that the application of a compressive dressing after TKA neither benefits nor harms the patient. Thus, compression dressings are no longer used for routine primary TKA.
Tsukada et al.[93]	105 patients	Prospective, randomized clinical trial	Advancing the time of the periarticular injection can provide a significant and clinically meaningful improvement in pain after TKA under general anesthesia.

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Table 1. Synthesis of assessed studies, in chronological order, their methodological differences and conclusions. São Paulo, Brazil, 2020 – continuation

Authors	Sample	Methodology	Conclusion
Jiang et al.[56]	147 patients above 65 years old	Controlled prospective study	The ERAS program is safer and more effective in elderly patients with TKA compared to the traditional via. It relieves perioperative pain, improves joint function, and reduces blood transfusion, length of hospital stay, and overall complications without increasing short-term mortality.
Iseki et al.[49]	47 patients	Randomized clinical trial	The addition of percutaneous periarticular injection of multiple drugs the day after TKA may provide better postoperative pain relief. More studies are needed in order to confirm the safety of percutaneous injection.
Yu et al.[87]	88 patients	Randomized clinical trial	The combined administration of CATXA + Dexa significantly reduced postoperative CRP and IL-6 levels, relieved postoperative pain, improved the incidence of PONV, provided additional analgesic and antiemetic effects, reduced postoperative fatigue, and improved ROM, without increasing the risk of complications in primary TKA.
Maniar et al.[88]	105 patients	Prospective, randomized study	A suction drain significantly reduced opioid consumption during the first 6 hours after TKA. The drain use made no difference to functional outcome at one year postoperatively. Clinical parameters such as swelling, infection and deep vein thrombosis also remained the same.
Laoruengthana et al.[43]	48 patients	Randomized clinical trial	Reduction of POP and functional recovery from SBTKA with early and late administration of PAMDI were not significantly different. The time interval of PMDI between knees did not confound the comparison between POP and functional recovery in SBTKA.
Cicekci et al.[51]	80 patients with ages between 40 and 85 years submitted to unilateral TKA	Prospective, randomized clinical study	ACB-L was superior to PAI-L in treating pain after TKA; however, PAI-L was superior to ACB-L regarding postoperative ROM and walking capacity.

TKA = total knee arthroplasty; POP = postoperative pain; CFNB = continuous femoral nerve block; SMI = subarachnoid morphine infusion; SpO2 = oxygen saturation; Mg = Magnesium; CIAA = continuous intra-articular analgesia; IL-6 = interleukin 6; IV = intravenous; NP/CS = nociceptive to neuropathic symptoms/central sensitization; ACB = adductor canal block; LIA = local infiltration analgesic; SPC = sciatic psoas compartment; PALI = periarticular local infiltration; PAI-L = periarticular levobupivacaine infiltration; KS = Knee Score; FS = Function Score; FS = frozen sections; PPOP = persistent postoperative pain; GPA = global patient assessment; CRP = C-reactive protein; MBA = medial bicompartmental arthroplasty; FNB = femoral nerve block; VAS = visual analog scale; NSAID = nonsteroidal anti-inflammatory drugs; CACB = continuous adductor canal block; AEA = anandamide; 2-AG = 2-arachidonoylglycerol; OEA = oleoylethanolamide; PEA = palmitoylethanolamide; COOXN = oral combination of oxycodone-naloxone extended-release; IVPCA = intravenous patient-controlled analgesia; IFCB = iliac fascia compartment block; LB = liposomal bupivacaine; SST = sufentanil sublingual tablet; SNP = single nucleotide polymorphism; ROM = range of motion; ERAS = enhanced recovery after surgery; CATXA = combined administration of tranexamic acid; PONV = postoperative nausea and vomiting; SBTKA = simultaneous bilateral total knee arthroplasty; PAMDI = periarticular multimodal drug injection.
Source: Research data, 2020.

The objectives of the researches related to pain after knee arthroplasty are presented in table 2.

Table 2. Presentation of the research objectives related to pain after knee arthroplasty according to the studies' results. São Paulo, 2020

Objectives	Quantity	%
Surgical methodology	1	0.6
Physical activity	1	0.6
Fast-track protocol	1	0.6
Percutaneous stimulation	1	0.6
Type of intravenous infusion	1	0.6
Compressive dressing	1	0.6
Enhanced recovery	1	0.6
Suction drains	1	0.6
Periarticular infiltration time	1	0.6
Tourniquet use	2	0.6
Preemptive analgesia	3	1.8
Adductor canal block	4	2.4
Femoral nerve block	5	3
Drugs	35	21
Bupivacaine + parecoxib	1	0.6
Pregabalin	1	0.6
Parecoxib + femoral block	1	0.6

Continue...

Table 2. Presentation of the research objectives related to pain after knee arthroplasty according to the studies' results. São Paulo, 2020 – continuation

Objectives	Quantity	%
Drugs		
CIAA	1	0.6
Fentanyl	1	0.6
Ibuprofen + acetaminophen	1	0.6
Duloxetine	1	0.6
ACB	1	0.6
Sufentanil	1	0.6
Paracetamol	1	0.6
Ropivacaine	1	0.6
Oxycodone/naloxone	1	0.6
CFNB and CFNB + SMI	2	1.2
Magnesium sulfate	2	1.2
Gabapentin	2	1.2
Tranexamic acid	2	1.2
Dexamethasone	3	1.8
Morphine	3	1.2
Bupivacaine	3	1.8
Anesthetic infiltration	7	4.2

CIAA = continuous intra-articular analgesia; ACB = adductor canal block; CFNB = continuous femoral nerve block; SMI = subarachnoid morphine infusion.
Source: Research data. São Paulo, 2020.

DISCUSSION

This study presented several therapeutic alternatives with the purpose of solving or minimizing POP from TKA. The various results are effective and promising, but did not reach a consensus or gold standard[10] for pain treatment due to the researches presenting different methodologies and samples.

As for the analysis of the results, the present study found a large number of publications (clinical trials) on the subject, demonstrating the great interest of the medical community in solving POP. Another strength of this study is that these clinical trials are recent. The sample consisted of 14.705 patients of both genders, aged between 45 and 83 years. As for the countries of origin, it was possible to observe that the scientific interest on POP of TKA is present in the American, European, and Asian continent.

The treatment of pain after TKA is challenging and the recommendation is to assess combined treatments and individualized targeted treatments according to the patient particularities. In order to ensure therapeutic success it's necessary to evaluate the clinical and cost effectiveness of multidisciplinary and individualized interventions[35,36].

Techniques employed for pain minimization and early patient rehabilitation have been evaluated as effective, such as FNB and sciatic nerve block applied in TKA, which can obviously inhibit tourniquet reaction, maintain hemodynamic stability, reduce anesthetic dose and relieve POP[37], with lower pain scores after 24h and lower incidence of adverse effects and bleeding compared to subarachnoid morphine[38], providing more potent analgesia in the first six hours after the operation.

The quality of postoperative recovery was higher when[39] associated with less intense pain perception due to the ACB, thus promoting early mobility rehabilitation[40,41]. Periarticular infiltration is a viable and safe alternative to FNB for immediate postoperative pain relief after TKA[42,43]. Perineural dexamethasone improves postoperative analgesia[44].

ACB accompanied by intraoperative periarticular local anesthetic infiltration accompanied by analgesia the day after TKA is improved with a catheter inserted at the level of the midpoint between the anterior superior iliac spine and the superior border of the patella compared to a more distal insertion closer to the adductor hiatus[45]. Pain control after TKA was found to be better in patients treated with CACB compared to those treated with single-dose ACB. Patients treated with CACB also had better ambulation and functional recovery after TKA[46-48].

The addition of percutaneous periarticular injection of multiple drugs the day after TKA may provide better relief of POP, but more studies are needed to confirm the safety of percutaneous injection[49,50].

ACB-L was superior to PAI-L in the treatment of pain after TKA; however, PAI-L was superior to ACB-L with respect to postoperative ROM and walking capacity[51].

As for surgical approach techniques, the configuration of the catheter orifice did not influence the efficacy of CFNB in this setting: the quality of analgesia was similar, with no reduction in local anesthetic or morphine consumption and equivalent postoperative quadriceps weakness[52]. Feasibility suggests that for TKA, percutaneous ultrasound-guided SNP is feasible in the immediate perioperative period and may provide analgesia without the undesirable systemic effects of opioids or quadriceps weakness induced by local anesthetic-based peripheral nerve blocks[53].

Some studies discuss the technique of the intraoperative tourniquet for pain control. According to study[54], the hypothesis that rehabilitation-related outcomes would be improved without a tourniquet is not supported by their results. When comparing the results of the surgeries performed with and without a tourniquet, no clear benefit was observed for either, as the greater amount of pain exhibited by the non-tourniquet group was only evident for a short period, and the improved mobility in the latter was not observed at a clinically relevant level. The lateral via provided better postoperative lateral patellar tilt in valgus knee arthroplasties[55].

The ERAS Program is safer and more effective in elderly patients with TKA compared to the traditional route. It relieves perioperative pain, improves joint function, reduces blood transfusion, length of hospital stay, and overall complications without increasing short-term mortality[56].

As for drugs, intravenous administration of dexmedetomidine in the perioperative period decreases serum IL-6 levels postoperatively in patients submitted to bilateral TKA and has a postoperative analgesic effect[57].

Preemptive analgesia added to a multimodal analgesic regimen improved analgesia, reduced inflammatory reaction and accelerated functional recovery in the first postoperative week, but did not improve long-term function[58]. An alternative is preoperative home exercises that provided better preoperative KS and FS and improved knee scores up to six months postoperatively. However, at 12 months after operation there was no significant difference between the intervention and control group for the KS and FS[59].

The fast-track protocol for primary TKA showed significantly lower knee pain scores and improved functional outcome in the first 7 days after TKA compared to a regular protocol[60].

The continuous analgesia infusion pump, compared to the formal intermittent intravenous regimen, presented better pain control and perception, improving tolerance to physical therapy, and reducing, on average, 15h of hospitalization, consequently decreasing surgical cost[61].

Advancing the timing of periarticular injection can provide clinically significant improvement in pain after TKA under general anesthesia[62]. Continuous local anesthesia provides analgesic benefit for up to one month after surgery, but did not influence PPSP at six months. Better pain control in the first month was associated with a reduction in PPSP. Patients with higher expectations of surgery, higher baseline inflammation and a pessimistic outlook are more likely to develop PPSP[63]. The addition of corticosteroid to periarticular injection significantly decreased early POP. More studies are needed to confirm the safety of corticosteroid in periarticular injection[64].

Pregabalin showed no beneficial effects, but increased sedation and decreased patient satisfaction. Study[65] does not support routine perioperative pregabalin for patients with TKA.

Study[55] demonstrated that CFNB resulted in reduced pain and was associated with lower morphine consumption and better mobilization within 24h compared to SMI. This study showed no statistically significant differences between CFNB alone and CFNB + SMI.

The use of parecoxib + continuous femoral block provided superior analgesic efficacy and opioid-sparing effects in patients undergoing TKA[66]. In this context, intra-articular bupivacaine in combination with intravenous parecoxib may improve pain relief and reduce the demand for rescue analgesics in patients undergoing TKA[67]. Compared to postoperative CFNB analgesia alone, CFNB + PALI could relieve pain at rest and pain during passive movement after TKA to achieve 90° knee flexion[68]. Thus, some patients could improve the postoperative rehabilitation training[69]. In preemptive multimodal analgesia strategies, parecoxib sodium can significantly decrease the VAS score in the short term, relieve pain right after surgery, and does not increase the incidence of complications. Parecoxib sodium is a safe and effective drug in the perioperative analgesic treatment of TKA[10,70].

Intraoperative anesthetic and periarticular infiltration with multimodal drugs significantly relieved pain after surgery and reduced requirements for NSAIDs, improved patient satisfaction and joint ROM without apparent risks after TKA[71]. LIA with LB 266 mg plus bupivacaine significantly reduced opioid requirements and intensity of pain and significantly improved readiness and discharge satisfaction from zero to 24h after TKA compared to bupivacaine alone. These findings support the use of LIA with LB for TKA when early discharge is the goal[72]. In conclusion, these studies provide evidence that local anesthetic infiltration reduces chronic pain for up to 1 year after operation, suggesting that routine use of infiltration could improve long-term pain relief[73].

Authors[74] performed a meta-analysis of randomized clinical trials and concluded that local infiltration provides analgesia comparable to a FNB for patients undergoing TKA based on pain during rest and opioid consumption, but a FNB reduces pain on movement.

The use of 10mg dexamethasone 1h before surgery and repeated at 6h postoperatively can significantly reduce the postoperative CRP and IL-6 levels and the incidence of PONV, relieve pain, achieve an additional analgesic effect, and improve early ROM compared to the other two groups in TKA[75]. ACB does not relieve lateral knee pain in the early stage but provides similar analgesic effect and better early rehabilitation efficacy compared to FNB in patients undergoing TKA[75,76].

As for fentanyl, additional use showed no prominent increase in analgesic effect in the field of CFNB after TKA[77]. The use of combined ibuprofen and acetaminophen showed additional benefits in terms of improved pain scores only on postoperative day 3, fewer potential adverse events related to opioid use, and less opioid use when compared to ibuprofen alone[78]. Intravenous or oral acetaminophen do not provide additional analgesia in the immediate postoperative period when given as adjunct multimodal analgesia in patients undergoing TKA in the context of spinal anesthesia[79].

Studies indicate that subarachnoid morphine reduces POP in patients with TKA. Furthermore, activation of central opioid receptors negatively modulates endocannabinoid tone, suggesting that potent analgesics may reduce the stimulus for peripheral endocannabinoid production. This study is the first to document the existence of fast communication between the central opioid and peripheral endocannabinoid systems in humans[80]. Although in some patients CFNB is inadequate, a lower dose of subarachnoid morphine (0.035mg) in addition to CFNB has been shown to be effective, with minimal adverse effects[81].

The technique of SPC blockade with bupivacaine HCL has guaranteed greater hemodynamic efficiency in the perioperative period in high-risk elderly patients[82,83]. The use of LB and plain bupivacaine showed superiority over pain control strategies, but they were relatively equivalent to each other in direct comparison[84].

The use of sufentanil 30μg was effective and well tolerated in the treatment of moderate to severe acute POP[85], while the preemptive administration of oral gabapentin did not reduce POP, but attenuated IL-6 production on the first postoperative day[86].

The effect of adjunct gabapentin on multimodal postoperative analgesia is controversial[13,63,72]. The main mechanism of action of gabapentin is achieved in combination with the 21 subunits of voltage-dependent presynaptic calcium channels. The expression of these channels is up-regulated in the case of nerve injury. Furthermore, gabapentin can decrease the hyperexcitability of secondary nociceptive neurons in the dorsal horn[23].

The combined administration of tranexamic acid + dexamethasone significantly reduced the postoperative levels of CRP and IL-6, relieved POP, improved the incidence of PONV, provided additional analgesic and antiemetic effects, reduced postoperative fatigue, without increasing the risk of complications in primary TKA[87].

The presence of a suction drain significantly reduced opioid consumption during the first 6h after TKA. The use of a drain made no difference to functional outcome at one year postoperatively. With the use of tranexamic acid in TKA, total blood loss and the need for blood transfusion were not affected by the presence or absence of closed suction drainage or by the drain orifice used. Clinical parameters such as swelling, ROM, infection, and deep vein thrombosis also remained the same[88].

As for the use of Mg, there are controversies[89,90]. For authors[90], perioperative intravenous administration of Mg did not influence POP control and analgesic consumption after TKA. Further studies should be conducted with different intraoperative and postoperative pain protocols to increase the antinociceptive effect potential of Mg[89]. However, RCT studies[66,67] with 44 patients reported that magnesium sulfate administration significantly reduced POP and minimized the difference in pain intensity between the first and second surgery.

Another unsuccessful approach is the application of a compression dressing after TKA. The use of this technique didn't result

in any clinical improvement in limb circumference, ROM, or pain. Based on this study, the belief is that the application of a compressive dressing after TKA neither benefits nor harms the patient. Therefore, the authors[90,91] suggested not using compression dressings for routine primary TKA.

The RCT[92] with 20 patients showed that in the immediate postoperative period of TKA, patients receiving oral extended-release oxycodone/naloxone had better pain control than those receiving IVPCA morphine, with a similar degree of PONV.

The limitations of the present study are related to the quality of the sample, which is heterogeneous, and the methodology of the studies being different, in approach, duration and dose of drugs and duration of follow-up.

The "implications for clinical practice" variables reinforce the understanding that there are benefits to anesthetic infiltration and multimodal drugs in modulating POP in TKA.

The causes of chronic pain after TKA are still not fully understood, although research interest is growing and it's clear that this pain has a multifactorial etiology, with a wide range of possible biological, surgical, and psychosocial factors that may influence outcomes.

CONCLUSION

Several classes of local and systemic drugs, including NSAIDs, opioids, and local anesthetics have been used to fight the nociceptive component of POP, aid early rehabilitation, improve quality of life, self-esteem, and reduce hospitalization and hospital expenses.

AUTHORS' CONTRIBUTIONS

Márcia Carla Morete-Pinto
Conceptualization, Methodology, Writing - Review and Editing, Supervision, Visualization
Arthur Fogel Sousa-Correa
Data Collection, Conceptualization, Project Management, Research, Methodology, Visualization

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