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Review Article

Injection of local Anesthetic for Post-Operative Pain Management after Anterior Cruciate Ligament Surgery: a Systematic Review of RCTs

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Abstract

Background
Effective injection of local anesthetic for postoperative pain management after anterior cruciate ligament surgery in-created patients' satisfaction.

Objectives
To collect evidence from randomized controlled trials (RCT) on injection of local anesthetic for pain management after anterior cruciate ligament surgery.
Study Design Systematic review.

Methods
A systematic literature review was performed using Cochrane Library, PubMed, Web of Science and Embase up to 2021. The end research time was Jun. 30, 2021.RCTs comparing injection of local anesthetic for pain management to other methods or placebo were included.The Cochrane Collaboration Network risk bias assessment tool was used to evaluate the literature bias.

Results
A total of 22 RCTs met inclusion criteria: 15 with only intra-articular injection, 3 with only local infiltration analgesia, 1 with only peri-articular injection, 2 with combined local infiltration analgesia and intra-articular injection, and 1 with combined peri-articular injection and intra-articular injection. Local anesthetic injection, intra-articular injection and peri-articular injection provided equivalent analgesia to regional nerve blocks. Intra-articular injection could obtain the same effect as a single femoral nerve block at postoperative pain management after anterior cruciate ligament surgery. Continuous-infusion catheters of a local anesthetic provided adequate pain relief but have been shown to cause chondrolysis. An increase in acute postoperative pain was found with local liposomal bupivacaine compared with femoral nerve block in postoperative pain management. But after the acute postoperative period, there were no significant differences.
However, the occurrence of nerve irritation postoperatively was found to be higher in the femoral nerve block.

Conclusion
Injection of local anesthetic is an effective form of analgesia. Local anesthetic injection would provide equivalent analgesia to single-never block. Despite the vast amount of evidence on this topic, further research is needed to improve the effectiveness of postoperative pain management and minimize pain and opioid consumption.

Clinical Relevance
These results provide the effective available evidence from RCTs on injection of local anesthetic for post-operative pain management after anterior cruciate ligament surgery.

Keywords: anterior cruciate ligament（acl）; postoperative pain management; injection of local anesthetic; intra-articular injection; local infiltration analgesia

Introduction

As development and popularization of day surgery, anterior cruciate ligament reconstruction（ACLR）has been treated as day surgery in many countries. Therefore, as confirmed by previous studies, patients after ACLR suffered horribly postoperative pain, which prevents ACLR from becoming the day surgery. In arthroscopic ACLR postoperative pain management,the main sources of local anesthesia administration as follows: femoral nerve block, adductor canal block (ACB), or peri-articular infiltration of the knee joint. These analgesic methods were generally termed local infiltration analgesia (LIA) [4]. Nerve block is a effective method of pain management, but it not suit for day surgery. Femoral nerve block has been incriminated in cases of impaired postoperative mobility and falls. Meanwhile, the occurrence of nerve irritation postoperatively was found to be higher in the femoral nerve block. Continuous-infusion catheters of a local anesthetic provided adequate pain relief but has been shown to cause chondrolysis.

In fact, many of postoperative pain management options, the optimal approach is actually unknown.

To evaluate the analgesic availability of each postoperative pain management approach, we retrieved randomized controlled trials (RCT) of local injection for analgesia after arthroscopic ACL surgery and conducted a systematic review. We aimed to clarify the postoperative analgesic efficacy of various local injection approaches of narcotic analgesia and even to find an optimal postoperative analgesic regimen for this procedure.

We registered the system reviewer in https://www.crd.york.ac.uk. ID:CRD42021244080

Materials and Methods

Literature inclusion criteria

(1) object of study; Primary ACL reconstruction, performed in adult patients, ASA class

Ⅰ～III（include III）, undergoing primary arthroscopic ACL reconstruction.

(2) study type : available published, randomized controlled trials (RCTs), defined in English.

(3) study subjects: in the experimental group or control group were treated with at least one of the previously described postoperative analgesic modalities (intra-articular injection, peri-articular injection, femoral nerve block, adductor canal block),

(4) described at least one of the primary or secondary outcome measures set by this

Systematic Review.

Literature exclusion criteria

(1) Duplicate published literature

(2) ASA class greater than III

(3) age less than or equal to 12 years

(3) non-primary surgery

(4) non-elective surgery

(5) systematic review and meta-analysis

(6) non-English literature

(7) non-human trials or animal experiments

(8) literature with unclear data description, incorrect statistical methods, or data presented that cannot carry on systematic review.

Outcome Measures

(1) Main outcome measures: postoperative VAS or NRS scores at any time point postoperatively.

(2) Secondary outcome measures:

1) the consumption and frequency of rescue analgesics /Supplementary analgesics during the postoperative period, the total consumption of postoperative opioid analgesics (eg. Tablet morphine, fentanyl, oxycodone hydrochloride, morphine, etc.) or nonsteroidal analgesics(ketorolac, tablet acetaminophen, etc.)

2) the postoperative knee movement (the measure was a range of motion at the physiotherapy control)

3) postoperative local and systemic adverse effects

4) Patients'pain management satisfaction or patients' satisfaction.

literature search

We searched the Cochrane Library, PubMed, Web of Science, and EMBASE databases by computer. The retrieval time is limited to 2021. The keywords were "anterior cruciate ligament", "postoperative pain management", "injection of local anesthetic", "intra-articular injection " and "local infiltration analgesia ". Study type was limited to a randomized controlled trials. Two researchers independently screened the literature and extracted the data. In case of disagreement, a third person would discuss and solve it.

Literature quality evaluation

The risk of literature bias was assessed by two researchers using the criteria provided by Cochrane Handbook of systematic review (version 5.1.0) (included in Review Manager 5.4), including random allocation method, allocation concealment, blind method, lost follow-up report, and other biases. When the two researchers had different opinions, the third person participated in the discussion and made a decision together. If all the criteria are low risk, it is a low risk of bias. Which has the highest quality; If one or more types of risk are unknown, it is an unknown risk of bias. Which has a medium quality; If one or more types of high risk, it is a high risk of bias. Which has the lower quality. At the same time, the Jadad scoring method was used to evaluate the quality of the included literature.

Result

Search Results

A total of 685 literatures were obtained from the initial screening, and 446 literatures remained after the removal of duplicates according to the inclusion and exclusion criterias. Whereafter, 396 literatures were removed because of irrelevant to the cases. There were 50 literatures were available for full text. In these 50 literatures, 4 meta-analyses and systematic review, 9 non-human experiments, 9 nerve blocks alone, 2

infant, and 4 academic artifacts literatures were eliminated. Finally, total of 22 RCTs met inclusion criteria: 15 with only intra-articular injections, 3 with only local infiltration analgesia , 1 with only periarticular injection , 2 with combined local infiltration analgesia and intra-articular injections and 1 with combined periarticular injection andintra-articular injections.A PRIMSA flow diagram is presented in Figure 1

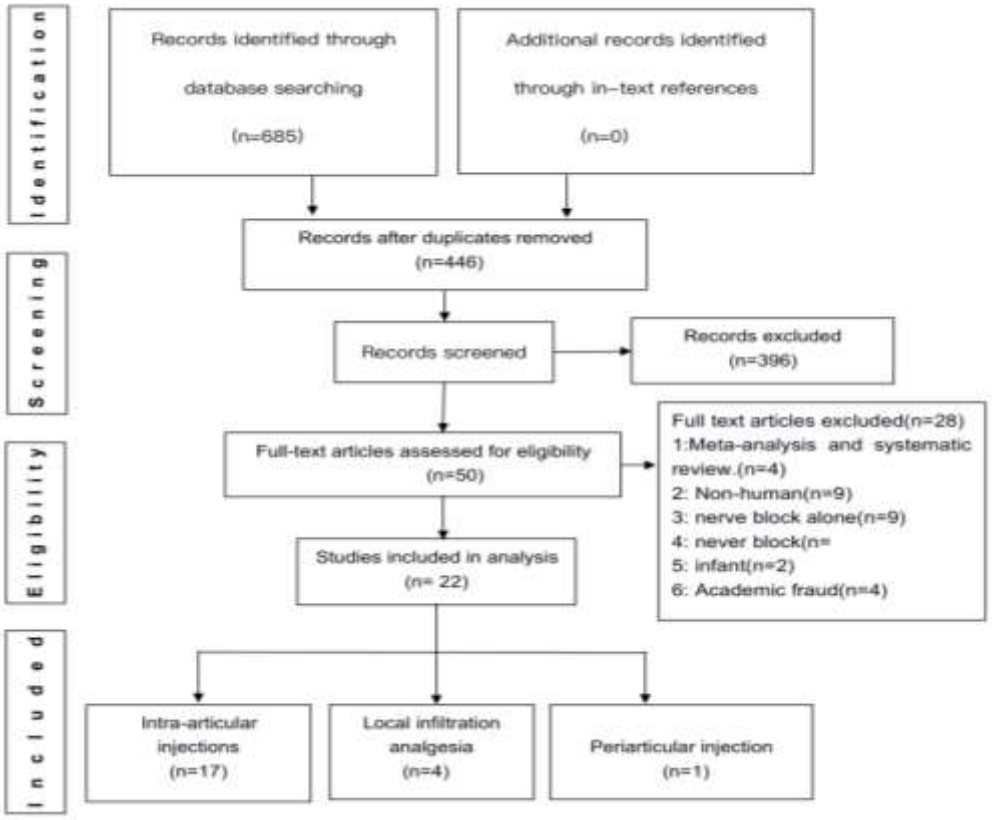


Figure 1: Flow diagram of study selection

Basic information of included literature

Basic information regarding patient demographics and characteristics of the included studies is presented in Table 1. A total of 1757 patients were included in this systematic review and there was a predominance of male patients in all studies. The mean age of patients ranged from 24 years to 36.7 years. And details of the intervention and outcomes of the included studies are presented in Table 2.

Author(year)	Study design	Anesthesia	Jadad	Level of evidence	No. of patients	Gender(F/M)	Mean age/(G1/G2/G3)	surgery
Lee(2020)	RCT	Not mentioned	7	1	47	6/41	-	ACLR
Chiang(2019)	PCS	Not mentioned	5	2	304	56/244	25.1 ± 8.1/30.3 ± 9.0	ACLR/ACLR+PM/ACLR+meniscus repair
Stebler(2019)	RCT	GA	6	Not mentioned	104	28/70	-	ACLR
Kurosaka(2017)	RCT	GA	5	1	129	74/56	29 (26, 31) /28 (25, 30)	ACLR
Sonnery-Cottet(2016)	PCS	GA	3	3	158	43/115	27.1±12.3/25.5 ±10.8	ACL/AXL+ALL
Okoroha(2016)	PCS	Not mentioned	5	1	85	33/49	27.85 (9.8) /30.5 (11.2)	ACLR
Kristensenr(2013)	RCT	GA	6	1	60	15/40	27/27.6	ACLR
Hosseini(2011)	RCT	GA	6	1	60	0/60	29.3 (7.7) /25.6 (6.7)	ACLR

Koh(2012)	RCT	Not mentioned	4	1	100	17/83	25.3 ± 4.7 /25.3 ± 4.1/25.2 ± 4.3	ACLR
Senthilkumaran(2009)	PCS	GA	6	Not mentioned	60	9/51	-	ACLR
Armellin(2008)	PCS	GA	6	1	120	27/93	30 (17–42) /28 (18–40)	ACLR
Parker(2007)	RCT	GA	5	1	63	31/32	30.5 (15-53) /30.1 (15-50)	ACLR
Stewart(2005)	PCS	GA	3	1	65	7/58	33.5(18-49)	primary ACLR
Vintar(2005)	PCS	SA	5	Not mentioned	39	7/31-	29.9 ± 7.63 /30.3 ±5.9/26.9 ± 5.9	ACLR
Alford(2003)	PCS	Not mentioned	6	Not mentioned	49	19/23	35±6/27±9/30±7	ACLR
Guler(2002)	PCS	GA	4	Not mentioned	42	1/41	-	ACLR
Hoenecke(2002)	PCS	Not mentioned	6	Not mentioned	26	7/19-	26.6±5.7 /27.0±6.3/26.2±6.2	ACLR
Butterfield(2001)	PCS	GA	4	Not mentioned	24	-	36(24-46)/36.7(25-49)	keen ligament reconstruction
Brandsson(2000)	RCT	GA	4	Not mentioned	40	14/26	30±7/33±10	ACLR
Tetzlaff(1999)	RCT	GA	5	Not mentioned	30	-	24(16-43)	ACLR
Karlsson(1995)	PCS	GA	5	Not mentioned	40	16/24	-	ACLR
Joshi(1993)	RCT	GA	4	Not mentioned	20	-	24(18-32)	ACL repair
RCT,randomized controlled trial;PCS, prospective comparative study;GA,general anesthesia;M,male;F,female.								

Table 1: Patient demographics and characteristics of the included studies.

A, The patient's VAS or NRS score at any time point postoperatively;

Table 2: Summary of interventions and outcomes of the included studies.

Author(year)	Assessment methods	Analgesic modalities	Drugs	Outcome measures	Result
Lee (2020)	VAS	intra-articular	NO	A,C	IA TXA had no effect in reducing postoperative pain.
			Tranexamic acid		
Chiang (2019)	VAS	intra-articular	NO	A,C	IA TXA had significantly lower VAS scores on postoperative day 3， and no difference on week 4.
			Tranexamic acid		
Stebler (2019)	NRS	donor site	ropivacaine 0.5%	A,B,C,D	AGB had lower resting pain scores at 48 hours after operation than LIA , but no difference at 2 hours and 24 hours
		AGB	ropivacaine 0.5%		
Kurosaka (2017)	VAS	periarticular	ropivacaine	A,B,E,F	PI had lower pain (VAS) scores at rest at 24 hours after surgery,and lower VAS score at 4 hours ,8 hours and 2 days than FNB
		FNB	ropivacaine		
Sonnery-Cottet(2016)	VAS	intra-articular	ropivacaine	A,B,F	IA and HDS had no signicicantly difference in reducing postoperative pain after ACL reconstruction ,in day0 (immediately after surgery)and day1
		hamstring donor-site	ropivacaine		
Okoroha (2016)	VAS	donor site	Liposomal bupivacaine	A,B,F	LIA(LB group)had high pain(VAS)scores in 5 and 8 hours postoperatively,but no difference in other times
		FNB	Liposomal bupivacaine		
Kristensenr (2013)	NRS	donor site	ropivacaine and epinephrine	A,B	LIA and FNB are comparable in the management of postoperative pain after ACL reconstruction ,at 0 hours,3 hours 24 hours and 48 hours
		FNB	ropivacaine		

Hosseini (2011)	VAS	intra-articular	isotonic saline	A,B,C	IA morphine and bupivacaine has lower pain scores on postoperative hour 2,hour 4 and hour 24.
			10 mg morphine sulfate and 0.5% bupivacaine		
			100 mg tramadol hydrochloride and 0.5% bupivacaine		
Koh (2012)	VAS	intra-articular	ropivacaine	A,F	IA injection have no value in pain relief after ACL reconstruction;PA MDC group and IA+PA MDC group had lower pain scores during the night after surgery.
		periarticular	multimodal drug cocktail (MDC)		
Senthilkumaran(2009)	VAS	intra-articular	bupivacaine morphine sulphate and bupivacaine	A,B	there were no significant differences in the VAS pain scores recorded in each groups after ACL reconstruction
Armellin (2008)	VAS	intra-articular	sufentanil,clonidine and ropivacaine	A,B,D	there were no significant differences in the VAS pain scores recorded in two groups after ACL reconstruction
			clonidine and ropivacaine		
Parker (2007)	VAS	intra-articular (continuous infusion)	no intra-articular catheter	A,B	there were no significant differences in VAS pain scores in each groups after ACL reconstruction
			bupivacaine		
			0.9% normal saline		
Stewart (2005)	NRS	intra-articular	bupivacaine,epinephrine and 0.9% normal saline solution	A,B,E	there were no significant differences in VAS pain scores in each groups after ACL reconstruction
			bupivacaine,epinephrine and methadone		
			bupivacaine,epinephrine and morphine		
Vintar (2005)	VAS	intra-articular (continuous infusion,PCA)	saline	A,B,C,D,F	there were no significant differences in the VAS pain scores recorded in each groups after ACL reconstruction
			ropivacaine and morphine		
			ropivacaine,morphine and ketorolac		
Alford (2003)	VAS	intra-articular (continuous infusion)	NO	A,B,C	The bupivacaine infusion catheter group has lower maximum pain and higher maximum pain after removal catheter than other groups; The placebo and bupivacaine infusion groups had lower median pain than no catheter group.
			saline		
			bupivacaine		
Guler (2002)	VAS	intra-articular	saline	A,B	Both tenoxicam and morphine groups had lower pain scores than the control group; tenoxicam group had lower pain scores than morphine group except 0.5 hours postoperatively.
			morphine		
			tenoxicam		
Hoenecke (2002)	VAS	the doner site	saline	A,B	The VAS pain score was consistently lower and the VAS pain relief score was consistently higher in the bupivacaine group.
			bupivacaine		
Butterfield (2001)	VAS	pre-surgical :intradermally,subcutaneously and periosteally at the anteromedial tibial incision site; intradermally,subcutaneously and periosteally at the lateral	NO	A,B,D,E,F	In the first 24 hr following discharge,there were no significant differences in pain scores in two groups after ACLR.
			saline		
			bupivacaine and epinephrine		

		femoral incision site; at the three portal sites;intra-articularly. post-surgical : around the tibial incision and the lateral femoral incision.			
Brandsson (2000)	VAS	intra-articular	saline	A,B,D	Preoperatively there were no differences in pain scores between the groups. After 24 hours, the pain scores were lower in the two intraarticular morphine treatment groups than in the control group. The pain score was significantly lower in the 5 mg intraarticular morphine group than in the intravenous and control groups during 24 hours to one week after surgery.
			5mg morphine sulfate(i.a.)		
		intravenous	1mg morphine sulfate(i.a.)		
			5mg morphine sulfate(i.a.)		
Tetzlaff (1999)	VAS	intra-articular(preoperative)	saline	A,B	In phase Ⅰ,bupivacaine with 1mg morphine group had lower pain scores on arrival at PACU (at 0 minutes) and at 30 minutes postoperatively, In phase Ⅱ,bupivacaine with 1mg morphine group had lower pain scores than other three groups on arrival at PACU(at 0 minutes) and at 30 minutes postoperatively;bupivacaine with 1mg morphine group and bupivacaine with 3mg morphine group had lower pain scores than other two groups at 120 minutes and 240 minutes postoperatively;bupivacaine with 3mg morphine group had higher pain scores than bupivacaine with 1mg morphine group on arrival at PACU(at 0 minutes) and at 30 minutes postoperatively.
			bupivacaine		
			bupivacaine,morphine		
Karlsson (1995)	VAS	intra-articular	saline	A,B	In all active treatment groups the overall pain scores were lower than in the control group . The VAS score was significantly lower for the morphine group only after 24 and 48 h, and for the bupivacaine group after 2, 4 and 6 h. For the bupivacaine/morphine group, the VAS score was significantly lower throughout the whole postoperative observation period.
			morphine		
			bupivacaine		
			bupivacaine with morphine		
Joshi (1993)	VAS	intra-articular	saline	A,B	The VAS scores in the morphine group were significantly lower at all times as compared with the control group.
			morphine		

or non-steroidal analgesics（including ketorolac、tablet acetaminophen）;

C,Mobility of the knee joint after surgery（measure was range of motion at the physiotherapy control）;

D, Post-operative local and systemic adverse effects（including vertigo, nausea, vomiting）

E, Other post-operative complications ;

Literature bias evaluation

In this paper, the Cochrane Collaboration Network risk bias assessment tool was used to evaluate the literature bias. The 22 included literature [1-22] all adopted the random method among which 10 literature [1-5,14,15,17,19,21] reported the method of random sequence generation, and realized the allocation concealment, so the selective bias was small; the 5 included literature [1,3,6,14,22] did not describe whether to use the blind method and to achieve the blind evaluation of research outcomes. The outcome data of 22 literature [1-22] were complete and there was no selective report of research results, so the follow-up and publication bias was small; no other bias was reported in the literature. (Figure 2-3)

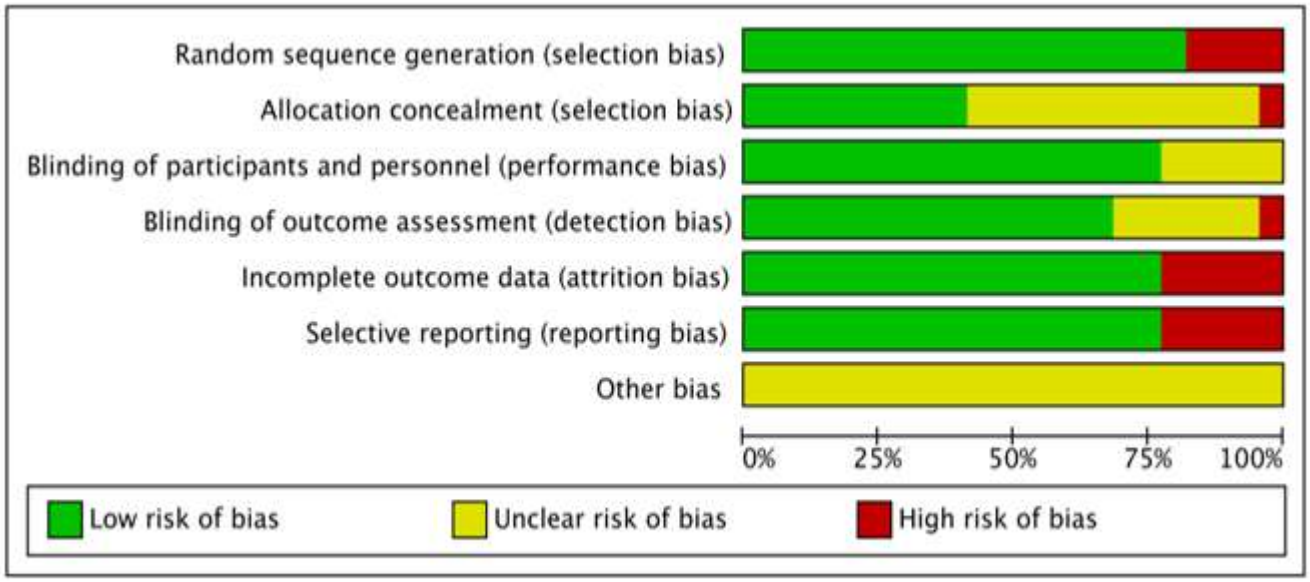
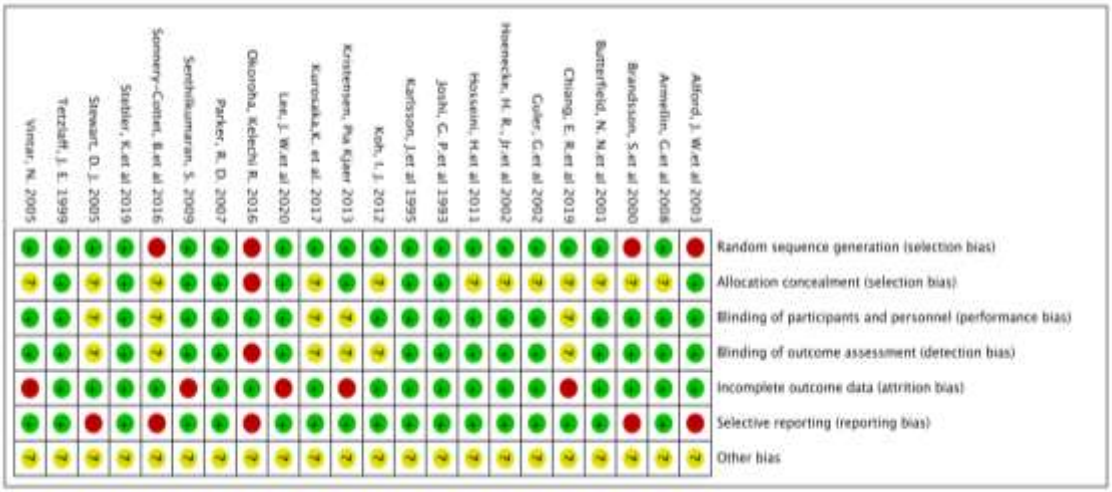


Figure 3. Risk of bias summary



Nerve block

As a common postoperative analgesic modality, the nerve block is widely used after various types of surgery. The most commonly used nerve block way after arthroscopic anterior cruciate ligament surgeries are femoral nerve block (FNB) and adductor canal block(ACB).

Pia Kjaer Kristensen et al think that after anterior cruciate ligament reconstruction with

hamstring tendon graft , there was no significant difference in postoperative NRS pain scores between intra-articular local injection of anesthetics and femoral nerve block alone. There was also no significant difference in analgesic consumption during the 48 hours postoperatively. Although there was a trend to decrease opioid consumption in the femoral block group during the first 3 postoperative hours, the trend was not significant[1].

Kelechi R. okoroha et al. refined groups of different graft sites in a trial when injecting local anesthetics. And they chose different injection sites depending on the site of graft taken. It was found that patients in the local infection anesthesia (LIA) group had significantly higher acute pain at 5-8 hours postoperatively than those in the FNB group. However, when statistical analysis was performed, it was found that the mean postoperative pain level and the postoperative morphine consumption equivalents in both groups did not differ significantly[2].

Kenji Kurosaka et al. found that patients who received a peri-articular injection of local anesthetics have lower pain scores at rest in the first 24 hours, 4 hours, 8 hours, and 2 days after surgery. In addition, patients consumed fewer opioids in the first 24 hours postoperatively at the latest. Nevertheless, Opioids related complications did not differ significantly between patients assigned to the two modes of analgesia[3].

Although the postoperative analgesic efficacy of FNB is precise. And it can provide comparable analgesic effect to intra-articularly injection of local anesthetic drugs into and local infiltration anesthesia at the graft site. But there is the non-negligible side effects of FNB, such as prolonged quadriceps inhibition,**[2]** prolonged sensory disruption in the anterior proximal high**[2].**

Although the postoperative analgesic efficacy of FNB is precise. And it can provide comparable analgesic effect to intra-articularly injection of

local anesthetic drugs into and local infiltration anesthesia at the graft site. But there is the non-negligible side effects of FNB, such as prolonged quadriceps inhibition,[2] prolonged sensory disruption in the anterior proximal high[2].

So, it is of particular importance to select a postoperative analgesic modality that can both provide equivalent postoperative analgesia and circumvent the various side effects associated with FNB.

After researching, Kevin stebler et al. indicated that ultrasound-guided adductor canal block (ACB) and local infiltration analgesia did provide equivalent analgesic effect after ACLR surgery. Meanwhile, they found that the consumption of intravenous morphine analgesics within 24 hours after the operation is similar. And there is no significant difference in both secondary pain and functional related results. Although the resting pain score in 48 hours after surgery is lower in the ACB group, the authors believe that it is likely to be related to one type of statistical errors.[4]

That is to say, the difference in resting pain scores found in this study, which credibility is needed to be weighed.

In other words, ACB can provide the same postoperative analgesic effect as FNB and make up for the defect of femoral nerve block caused by FNB, which makes ACB a better choice than FNB, especially after arthroscopic anterior cruciate ligament reconstruction surgery.

Although nerve block is widely used in clinic, through our systematic review of a large number of literatures, local infiltration anesthesia can provide equivalent postoperative analgesia and avoid the side effects related to nerve block. This may suggest that local anesthesia is a better choice in the future clinical practice.

The donor site injection

As we all know, there are differences in the details of the arthroscopic anterior cruciate ligament reconthe tendon donor site. So, is local anesthetic injection at the corresponding tendon donor site a possible choice for postoperative analgesia?

According to the study of Heinz R. hoenecke et al., continuous injection of local anesthetic (0.25% bupivacaine) at the donor site can significantly reduce

within 48 hours after the operation. And it can also reduce the dosage of opioid analgesics postoperatively.[5]

Pia kjaer Kristensen et al. found that the donor site postoperative analgesia effect with FNB. In their study, within 48 hours after the operation, the donor site injection group was superior to the FNB group in both postoperative pain score and postoperative pain relief. At the same time, the local anesthesia of the donor site injection can good to avoid the side effects of femoral nerve block.[1] Furthermore, the author even confirmed that local injection of local anesthetics at the graft site can achieve comparable postoperative analgesic effect with a femoral nerve block, which may reflect that the main source of pain after arthroscopic ACL surgery is the pain derived from the donor site. It may also lead us to think in another aspect that whether FNB can block the pain from the donor site or not.

Bertrand sonnery-cott et al. also found that the hamstring donor site injection and intra-articular local injection of narcotic drugs can provide similar postoperative analgesic effect. At the same time, there was no significant difference both in consumptions of opioid analgesics and in anesthesia related side effects.[6]

Kelechi R. okoroha et al. also used the local infiltration anesthesia of the donor site injection in their trial. But they came to the opposite conclusion.They found that the acute pain score of the donor site injection group was significantly higher than that of the FNB group in 5-8 hours after operation. However, this difference only exists in the postoperative acute pain period. After the acute pain period, the donor site injection can provide the comparative analgesic effect as FNB but avoiding the inherent risk of femoral nerve block. This may be related to the type of local anesthetic they choosed. Among the many local anesthetics, they chose liposomal bupivacaine as their local infiltration anesthetics. The author specifically points out in the article that they choose liposomal bupivacaine because of the delayed release from lipid storage delivery. Studies have shown that there is 10 hours lag time before optimal local concentration of liposomal bupivacaine.[2]

Kevin stebler et al. mainly compared postoperative morphine consumption. Morphine consumptions, resting and dynamic pain scores and postoperative nausea and vomiting at 2 hours and 24 hours postoperatively were comparable between experimental group and control group in their study. And there was no analgesic technique impacted either early or late functional outcomes.[4]

Intra-articular injection

Through our systematic search of literatures, we found that intra-articular injection of drugs for pain management after arthroscopic ACLR surgery was mentioned in the literature as early as 1993[7]. From 1993 to 2020, scholars from different countries and regions continued to explore the postoperative analgesia of intra-articular injection.

The injected drugs are different, including morphine alone, local anesthetics alone (bupivacaine, ropivacaine), combined local anesthetics with morphine or other opioid analgesics, combined local anesthetics with non-steroidal analgesics, and a new drug combination method , multimodal drug cocktail (MDC), etc. In addition, some recent studies have explored the postoperative analgesic effect of intra-articular injection of tranexamic acid.

At the same time, the way of injection is not same. Such as indwelling catheter for continuous infusion of drugs, single injection of drugs and so on.

After systematic analysis of literatures, we found that intra-articular injection of morphine can produce exact postoperative analgesic effect, which was confirmed by GP Joshi et al. In 1993. They found that patients in the intra-articular morphine group had lower postoperative VAS pain scores than those in the intra-articular saline group[7]. Later, in the study of s brandsson et al., the optimal dose of intra-articular injection of morphine was explored in more details. They found that the postoperative VAS pain scores was significantly lower in patients with intra-articular injection of 5 mg morphine than in patients with intra-articular injection of 1 mg morphine. What's more, they found that the postoperative pain scores of patients who received intra-articular injection of 5 mg morphine from 24 hours to 1 week after operation was continuously lower than that of patients who received intravenous injection of 5 mg morphine.[8] It seems to suggest that the analgesic effect of applicating morphine locally is better than applicating morphine systemically . It does support the view that the analgesic effect caused by intra-articular morphine is a local effect in the peripheral tissue in the site of injection.[8]

In comparison with non-steroidal analgesics , tenoxicam, Guler g et al. found that intra-articular injection of tenoxicam and intra-articular injection of morphine can also significantly reduce the postoperative VAS scores[9]. Although the VAS scores of patients in the tenoxicam group was continuously lower than that in the morphine group within 48 hours after operation, the difference has statistical difference only within 30 minutes after surgery. However, based on the fact that the patients in the tenoxicam group require less supplementary analgesic drugs in and 6 hours after operation than who in the morphine group, the article finally points out that tenoxicam can provide better analgesic effect than morphine.[9] This also leads to our thinking that non-steroidal analgesics may be a more selective option for morphine in postoperative pain management after arthroscopic ACLR surgery.

Since the advent of morphine, medical workers have been enthusiastic about its research. While intra-articular injection of morphine alone has been widely studied, the injection of morphine combined with local anesthetics is also the focus of medical workers. In the literatures we included, researchers chose bupivacaine with morphine, ropivacaine with morphine, added a non-steroidal analgesics or even an antibiotic. For the arrangement and combination of different drugs, of course , people's starting point is to integrate the advantages of various drugs and minimize their respective side effects. Previous studies have shown that the onset time of morphine is generally 3-6 hours after surgery[9]. So, if morphine can be combined with fast acting drugs, it can theoretically reduce the

pain of patients 3-6 hours after surgery. After a systematic review of the literatures, we found that bupivacaine with morphine, tramadol hydrochloride, methadone and ropivacaine with morphine, ketorolac, clonidine, sufentanil, and even **KOH**'s multimodal drug injection can significantly reduce the postoperative VAS scores. First of all, the combination of local anesthetics and morphine dose improve the pain scores in the early postoperative period, but there was no significantly difference in VAS or NRS scores between local anesthetics combined with various drugs. In addition, the increase in the variety of mixed drugs did not increase the analgesic effect of postoperative analgesia. And it also did not increase the incidence of postoperative adverse reactions. This may suggest that the combination of rapid onset local anesthetics with slow onset opioid analgesics or non-steroidal analgesics can achieve satisfactory analgesic effect.

However, in the study of the mixture of local anesthetics and morphine, the conclusion in a literature seems to be in contradiction with the conclusion of Brandssons[8] .Brandssons found that the VAS pain scores of patients with intra-articular injection of 5 mg morphine was significantly lower than that of patients with intra-articular injection of 1 mg morphine[8]. It seems that with the increase of morphine dosage, the postoperative analgesic effect will be enhanced. However, the study of Tetzlaff, J. E. found that patients given 3 mg morphine had higher pain scores at 0 minutes and 30 minutes after operation than those given 1 mg morphine.[11]They combined bupivacaine with morphine, and they finally found that bupivacaine with 3mg morphine group had higher pain scores than bupivacaine with 1mg morphine group at 0 minutes and at 30 minutes postoperatively[11].

However, the specific reasons for this result have not been clarified, which provides a new idea for our future research work. Perhaps we can explore the optimal intra-articular dose of morphine from the perspective of the hypothesis of peripheral opioid activation.

The specific analgesic mechanism of intra-articular local injection of morphine has not been clarified yet. The exact mechanism by which local opioids reduce pain after peripheral administration is not yet fully known . It is an urgent problem to be solved in our future research.

In addition to studies on the postoperative analgesic effects of intra-articular injection of analgesic drugs, there are also studies on the postoperative analgesic effects of intra-articular injection of local anesthetic drugs alone. Intra-articular injection of local anesthesia has focused on bupivacaine and ropivacaine.

According to the research of Alford, J. W.et al[12] , the bupivacaine infusion catheter group has lower maximum pain than other groups. But it has higher maximum pain after removal catheter than other groups. The bupivacaine infusion catheter patients had lower maximum pain than the placebo or control groups while the catheters are still in place. But it is unexpected that this positive analgesic effect was reversed after the catheter was removed. After the catheter was removed, patients in the bupivacaine group had higher maximum pain than other two groups.[12]

On the contrary, Parker, R. D. et al .[13] and Vintar, N. et al. [16] found that there was no significant difference in postoperative pain scores between patients with intra-articular bupivacaine group and control group.

In the study of Chiang, E. R. etal [14] and Lee, J. W. etal [15], they selected intra-articular injection of Tranexamic acid (TXA) to test whether it could relieve postoperative pain in patients undergoing arthroscopic ACLR surgery.

In the literatures we included, only two literatures mentioned the method of intra-articular injection of Tranexamic acid (TXA), but their conclusions were exactly the opposite. Chiang, E. R. et al,. found that intra-articular injection of TXA group had significantly lower VAS pain scores on postoperative day 3, and no difference on week 4[14]. However, Lee, J. W. et al. found that intra-articular injection of TXA had no effect in reducing VAS pain scores after ACLR surgery [15] . But, a consistent conclusion was reached in these two studies that intra-articular local TXA injection did reduce bleeding in patients undergoing arthroscopic ACLR surgery.(Table2)

Table 2. Summary of interventions and outcomes of the included studies

Discussion

Among the included literatures, 3 were provided for continuous analgesia [12] [13] [16]. In their study of continuous postoperative analgesia, they found that the psychological effects of patients also play a significant role in the experience of postoperative pain. This can be reflected in the changes in the pain experience of patients before and after remove the catheter. It suggests that the psychological comfort of patients is also very important. At the same time, bad psychological hints should not be given to patients not only before but also after surgery.

Alford, J. W. etal. especially pointed out in the end of their article that the data for median pain ratings suggest some element of placebo benefit of postoperative catheter placement in the joint . In other words, patients believed in the benefit of the catheter itself, rather than its contents. It may promote low narcotic consumption and high motivation to perform therapy tasks[12].

Meanwhile,It should also be noted that continuous infusion of anesthetic drugs with joint catheters, while providing adequate pain relief, has been shown to cause chondrolysis.

In the literature we included, all patients were given supplementary analgesics after surgery as needed (when the VAS pain scores was greater than or equal to 5) , in accordance with the requirements of medical ethics. Although the total dose of analgesic supplementation has been evaluated in the literature, whether the VAS pain scores or NRS pain scores measured at the later stage of analgesic supplementation can reflect the true analgesic effect of various postoperative analgesic methods remains to be discussed. The VAS or NRS pain scores obtained for all trials were based on a dose of supplemental analgesics. Although the consumption of supplementary analgesics was systematically evaluated in almost all experiments, the assessment methods of the consumption of supplementary analgesics were not identical in all the included literatures, so we could not draw a conclusion on the consumption of supplementary analgesics for reference.

Vintar, N. et al**.**pointed out that regarding of postoperative pain, their study was designed to be as comfortable for patients as possible. They emphasized this point at the end of their article. They think all patients accessed to morphine PCIA did provide satisfactory analgesia in the placebo group at rest and during physical rehabilitation. But this maybe explain why there are no statistically significant differences in pain scores among groups[16].

This is a general deficiency in these experiments, which is also a problem we need to solve in the future research work. But due to ethical considerations and patient-centered principles, it seems that we cannot simply for scientific purposes not give any additional analgesics when patients are suffering from severe postoperative pain. As we can imagine, this is a very bad medical experience for patients. This is the paradox of all clinical research.

What is clear, however, is that the consumption of opioid analgesics after intra-articular morphine injection is significantly reduced. However, the mechanism of the analgesic effect induced by the peripheral application of morphine is still not clear. Although some scholars have proposed the hypothesis of peripheral opioid receptors, the specific mechanism of the analgesic effect induced by the peripheral opioid receptors is still unclear. There have been studies to evaluate the analgesic effect of morphine with the active metabolite M6G in plasma.[8] After **S Brandsson** applied 5mg morphine in the articular space, the concentration of metabolite M6G in plasma was much lower than that of M6G after the same dose of morphine intravenous infusion. And it's nowhere near the level that would produce a systemic analgesic effect. This is not a good explanation for why the same dose of morphine injected into the joint cavity is so much more effective than intravenous injection of morphine. But one aspect of this is that the analgesic effect of the topical application of morphine to the peripheral tissues is not through systemic action but through the action of

the peripheral opioid receptors. But that still doesn't shed light on the mechanism. This is a very good inspiration for our future research work, we can carry out more in depth research in this aspect, and to explore the mechanism of peripheral opioid receptors activation.

It is still the aspect of intra-articular injection of morphine. All articles using intra-articular injection of morphine or opioids have come to the conclusion that intra-articular injection of morphine can not only reduce the consumption of postoperative morphine or opioids, but also reduce the systemic adverse reactions related to morphine or opioids, such as nausea, vomiting, dizziness, etc. This undoubtedly tells us that intra-articular local opioid analgesics is a better choice than systemic use of morphine after arthroscopic ACLR surgery. So, whether this way of administration can be extended to other knee joints operations or other joint operations, and whether the advantages of this way of administration still exist when applied to other situations, these are the problems that we need to solve in the future research work.

In addition, only non-English literatures were excluded in the literature screening process. In the included literature, none of the experiments made detailed classification and comparison on demographic characteristics such as gender, age, race and ethnicity. There was no significant difference in these demographic characteristics between all of the experimental group and the control group. But ,pain tolerance is known to vary across genders, ages, and ethnicities. Patients undergoing ACLR surgery are relatively young. This provides a clear research idea for our future research work. We can carry out more detailed grouping and research on the above factors, aiming to find individualized postoperative analgesia programs for different groups of people, so as to minimize the pain suffered by patients after surgery.

Conclusion

Injection of local anesthetic is an effective form of analgesia. Local anesthetic injections would provide equivalent analgesia to single-never block. Despite the vast amount of evidence on this topic, further research is needed to improve the effective of postoperative pain management and minimize pain and opioid consumption.

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