Prognostics of outcome of total knee replacement: on patient selection and intraoperative issues

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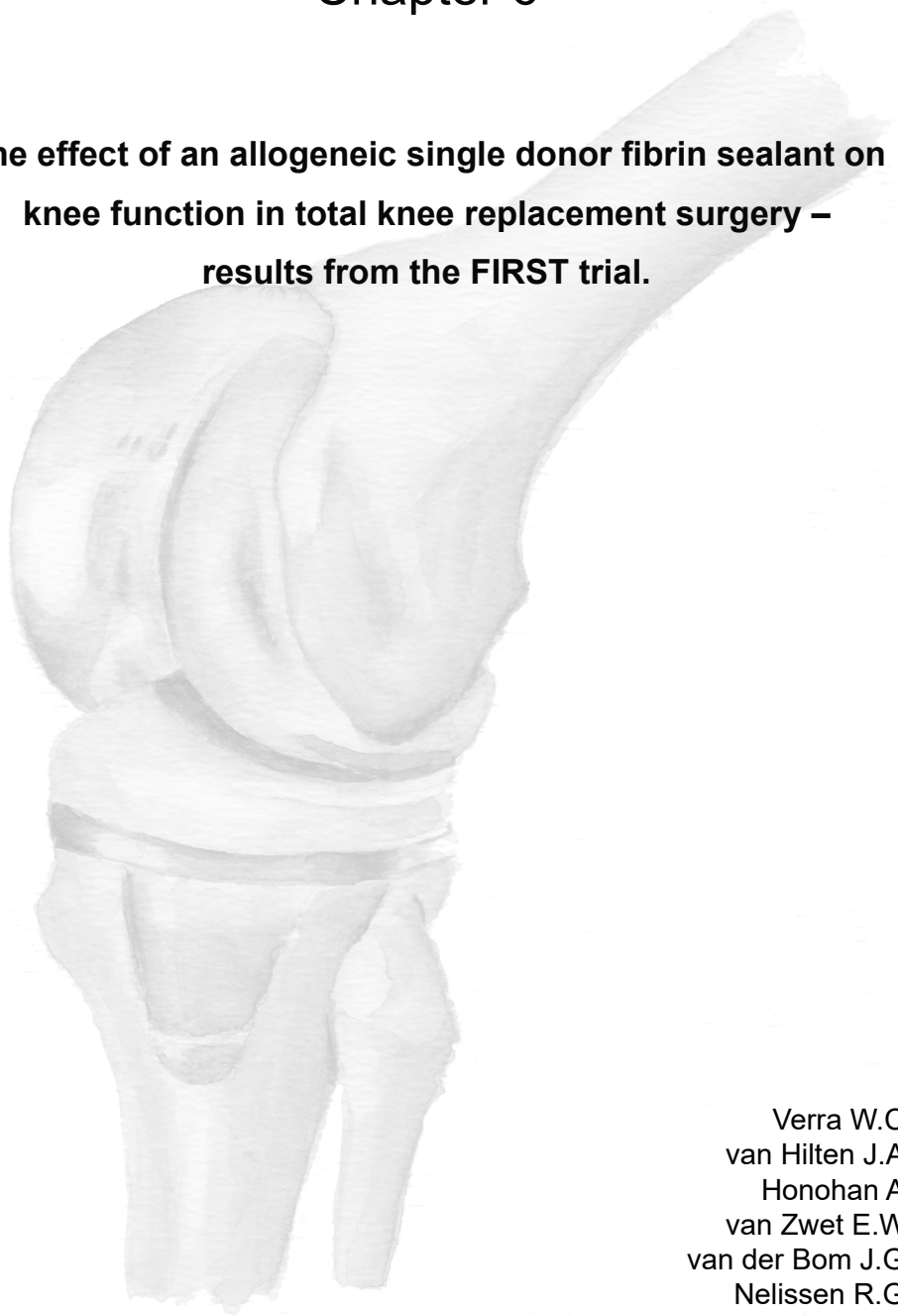
Chapter 6

The effect of an allogeneic single donor fibrin sealant on knee function in total knee replacement surgery – results from the FIRST trial.



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Abstract

Background. Total knee replacement (TKR) is increasingly performed in short term hospital stay, making same day mobilization an important issue after surgery. Little joint effusion, by reducing intra-articular blood loss, will enhance knee range of motion. The application of a topical fibrin sealant on the intraoperative bare bone and synovial tissue may contribute to better early full mobilization and thus improved functional outcomes. Since ambulation with a fully extended knee is less strenuous, we hypothesized that patients who received fibrin sealant would demonstrate improved early knee extension after six weeks compared to patients who received standard care.

Methods. A multicenter randomized controlled trial in a consecutive series of osteoarthritis patients scheduled for TKR surgery. Participants were randomized to receive fibrin sealant or not before closing the knee joint capsule. Primary outcome was change in knee extension angle (^{o}) at short term (2 weeks) follow-up (cExt). Secondary outcomes were 6 week extension angle, knee flexion angle, hemoglobin loss, blood transfusion rates, complication rates, the Knee Society Score, the KOOS and EQ5D scores.

Results. After six-week data were available from 250 patients an interim analysis was performed by an independent Data Safety Monitoring Board for safety and effectivity assessment. This interim analysis showed that sufficient patients were included to detect a cExt of 10^{o} between both groups. Inclusion was stopped but all, in the meantime, included patients were treated according to their randomization. A total of 466 patients were available for analysis.

Both groups were comparable in terms of baseline characteristics. The mean cExt was 0.2^{o} (95%CI -0.5 to 0.9). No differences in secondary outcomes were found.

Conclusions. No beneficial effects or side effects were found of a topically applied fibrin sealant during TKR surgery. These results discourage the clinical use of a fibrin sealant in TKR.

Introduction

The frequency of total knee replacement (TKR) for the treatment of osteoarthritis will increase in the coming years due to an aging population.[1] In the Netherlands the number of TKR increased by almost 25% between 2010 and 2015 to over 26.000 TKR's annually (www.lroi.nl). TKR is also increasingly performed in two-day or even one-day surgery, necessitating the need for immediate postoperative full ambulation and range of motion exercises. Since the latter is restricted by intra-articular blood loss, ways to control this loss are important for rapid patient recovery. The mobilization and weight bearing is less strenuous if full extension of the knee is present. On a more holistic patient level, these issues have also been shown to be related to patient blood management.[2-7] Earlier, our group demonstrated an average of 650-700 mL of overall (visible and non-visible) blood loss after TKR.[4] Reducing this blood loss will most likely benefit the TKR patient.

Theoretically, a fibrin sealant has the ability to reduce bleeding of surgically injured bone and synovial tissue by forming a sealing layer.[6] Several randomized studies report on the effect of fibrin sealant in reducing blood loss (i.e. hemoglobin level) and/or transfusion rates after TKR.[8-14] Since the introduction of modern transfusion trigger protocols transfusion rates have decreased tremendously and reducing transfusion frequency has therefore become a less relevant outcome after TKR. Outcome measures such as improvement of functioning and mobility are increasingly considered important, improving patient independence and satisfaction.

We designed a randomized controlled clinical trial to assess the effect of a topical applied allogeneic single donor fibrin sealant on functional knee recovery after TKR surgery. We hypothesized that patients who received this topical fibrin sealant intraoperatively would demonstrate improved clinical favorable early knee extension (primary endpoint) compared to patients who received standard care.

Methods

We conducted a single-blinded, multicenter randomized controlled trial at six orthopedic centers in the Netherlands. The study protocol was approved by the central medical ethics committee of the Leiden University Medical Center (P10.115) and registered at the Dutch Trial Registry (NTR2500). Local medical ethics committees approved the study protocol in all participating centers. A study independent monitor visited one of the centers to monitor legal-and protocol compliance.

Patients

Patients elected to undergo primary TKR between January 2011 and February 2013 for the treatment of primary osteoarthritis or rheumatoid arthritis were eligible to be included in the study. Exclusion criteria were age under eighteen years, ASA score >III, any coagulation disorders, no knowledge of the Dutch language, and unwillingness to participate. All patients provided written and signed informed consent before inclusion. Patients were randomized to receive either intra-articular topical Cryoseal™ fibrin sealant (CS) or standard care without an intra-articular hemostat.[15] A method of computer generated per-center randomization using permutated blocks with randomly differing block-sizes was used (ProMISe™ software; Leiden University Medical Center). Patients, all staff involved in data collection and data analysis and all authors were unaware of the treatment allocation.

Investigational Product

Cryoseal™ fibrin sealant (CS) is produced by Sanquin, the Netherlands.[15] CS is derived from one unit of fresh frozen plasma donated by a single donor. One unit of single-donor quarantined plasma yields between 10-15 mL CS from which two syringes were transported in a sealed bag. A fibrin sealant in general is composed of two main components, fibrinogen and thrombin that, when mixed together at 37°C results in a fibrin molecule clot.

Protocol of Surgery

All patients were operated on adhering to the study protocol. Type of anesthesia was not standardized. Tourniquet use during surgery was allowed; however, during the procedure the tourniquet was deflated in order to surgically coagulate injured vessels with electrocautery. Timing of deflation of the tourniquet was left to the orthopedic surgeons' preference. All participating hospitals were free to choose their own preferred brand and type of TKR implant. Cementation was left to the centers preference. The use of a drain was an important issue when the study was performed. We hypothesized that the use of drainage systems may interact with the effect of the CS. Orthopedic centers were therefore requested to perform the procedure either with or without vacuum drainage for all TKR procedures at that center.

For each randomized patient a cooling box was delivered to the operating room containing cooling elements and either CS or no CS. Before application the frozen CS was thawed at 40^{o}C for at least twenty minutes. The surgeon and scrub nurse were informed about the content of the box only immediately before application. Patients assigned to the CS group were treated with a maximum of 10 mL CS divided over two separate syringes, one with 5 mL and one with the remaining 3-5 mL. The use of at least 5 mL CS was mandatory. The CS was topically applied after placement of the implant on intra-articular tissues and bare bone surfaces. CS was applied with the use of a spray tip mounted on the syringe. The remaining 3-5 mL CS was used at the discretion of the surgeon. The knee was closed routinely. All unused CS and empty syringes were returned to the local blood transfusion department where the amount of CS applied to each patient was recorded. Standard care was considered TKR according to this protocol without the use of CS.

After surgery all patients received a low molecular weight heparin thrombosis prophylaxis during six weeks. All patients followed a regimen of full weight-bearing physical therapy.

Transfusion policy

Decisions regarding perioperative blood transfusion were made by the attending anesthesiologist and/or orthopedic surgeon, similar guidelines were in place in all participating hospitals. The transfusion protocol is presented in the Appendix.

Data collection

Data were transcribed onto Case Report Forms (CRF's) by research nurses who were unaware of the randomization result. All written data were transferred from the CRF to the secure web-based data management system (ProMISe^{TM}).

Outcomes

Primary outcome was the change in knee extension (cExt) angle (^{o}) at short term follow-up (i.e. after two weeks) compared to the preoperative knee extension. Secondary outcomes were the six week cExt, the knee flexion, perioperative blood (hemoglobin) loss, transfusion rates, postoperative pain, complications (superficial and deep infection, hematoma, and systemic complications), and total duration of hospital stay. Furthermore the Knee Society score and validated patient reported outcome scores; the Dutch versions of the Knee Injury and Osteoarthritis Outcome Score (KOOS)[16] and the EQ5-D[17] were recorded. Outcomes were recorded at baseline and 2- 6- and 52 weeks after surgery.

Sample size

A sample size calculation was performed for our primary outcome which is cExt two weeks after surgery. A difference between study arms of 10^{o} was expected and was also considered clinically relevant. Because of scarcity of data to base our calculations on, based on the date from a trial registered on clinicaltrials.gov (NCT00492219) a standard deviation of 35 degrees was assumed. The sample size needed to detect a difference of 10^{o} with a t-test assuming equal standard deviation in both groups of 35 is 259 per group (using the O'Brien-Fleming rule for one interim analysis. Because of the scarcity of data during development of the study protocol a re-estimation of the sample size was specified in the protocol after the first 250 inclusions were completed.

Interim analysis

According to the protocol a single interim analysis was conducted by an independent Data Safety Monitoring Board (DSMB) when 2-week follow-up data were available from 250 patients (because of overshoot this turned out to be N=262 included in interim analysis). The interim analysis was intended as both a safety assessment and superiority analysis as well as used to re-estimate the sample size.

Ultimately an interim analysis of the first 262 evaluable patients was performed. All (serious) adverse events were recorded. The DSMB judged whether an adverse event was possibly related to treatment with CS. The DSMB was blinded to group allocation when assessing the data. The standard deviation of cExt between baseline and 2 weeks was 7.7 according to the interim analysis. It was concluded that in the study protocol the standard deviation of the primary outcome was over-estimated. According to this new sample size calculation there was already enough power to stop inclusion. However, because the protocol stated at least 400 patients were to be included, it was decided to continue until this amount was reached. Ultimately over 400 patients were included because of overshoot of inclusion.

Statistics

Descriptive statistics are reported as number and percentage for categorical variables. Normally distributed continuous variables are reported as mean and standard deviation and non-normally distributed continuous variables as median and inter-quartile range.

Primary outcome

A repeated measure linear mixed model was used to assess the difference in cExt between patients randomized for Standard Care and CryoSeal fibrin sealant, adjusting for pre-operative knee extension angles (crude model). The model was adjusted for any misbalance in baseline characteristics between the randomized groups (Model 1). To investigate whether the CS effect was modified by the use of a drain, drain use and the interaction between drain use and CS versus standard care was added to the model (Model 2).

Secondary outcomes

For the secondary outcome change in knee extension after 6 week and for change in knee flexion, the same repeated measurement analysis of covariance was performed as for the primary outcome adjusting for preoperative knee flexion. EQ5D and VAS were compared by mean and interquartile range for both randomization groups pre-operatively and after six weeks of follow-up.

Analyses were carried out according to the intension-to-treat (ITT) principle. Difference in estimated mean differences between CS and Standard Care arms and their 95% confidence intervals were computed with the Standard care arm as a reference group. Statistical analysis was performed with computer software (SPSS 20.0 for Windows, SPSS Chicago, IL.). Statistical tests were two sided, a p-value of <0.05 was considered statistical significant.

Results

A total of 498 patients were randomized between January 2011 and February 2013. From these patients a total of twenty-four (twelve patients in each study arm) ultimately did not undergo TKR surgery or withdrew their informed consent (IC). A further four eligible patients (3 in CS arm and 1 in control arm) gave IC twice and were included by randomization for a second TKR at least three months later on the contra-lateral side. Eight patients who underwent TKR were excluded for analysis due to the missing cExt data pre- or postoperatively.

A total of 466 patients were available for analysis; 232 in the CS arm and 234 in the control arm (Figure 6.1). Due to random logistical reasons with the different clinics no exact total of patients who were eligible can be presented.

Figure 6.1: Flowchart of patient inclusion

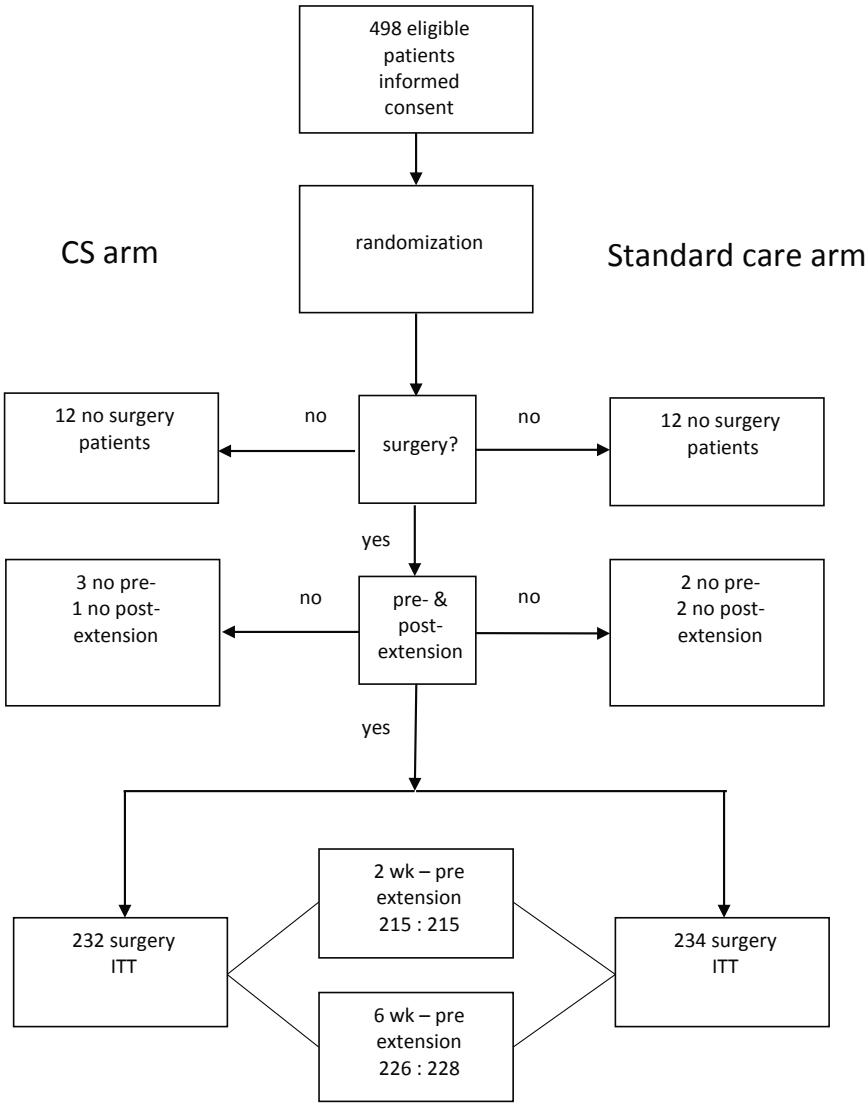

Table 6.1: Characteristics of participants

	Standard Care	CryoSeal
Baseline variables		
Number of patients	234	232
Females N (%)	152 (65)	148 (64)
Age years (SD)	68 (9)	68 (10)
Body mass index kg/m^2 (SD)	29 (5)	29 (5)
ASA score *N (%)*		
I	44 (19)	32 (14)
II or III	182 (78)	185 (80)
Associated co-morbidity *N (%)*		
Diabetes Mellitus	47 (20)	31 (13)
Type of OA *N (%)*		
Primary OA	215 (92)	203 (88)
Preoperative variables		
Hemoglobin g/dL mean (SD)	13.8 (1.3)	13.7 (1.4)
Pain score 0-10 median (IQR)	7 (5 to 8)	7 (5 to 8)
Knee extension angle ^{0} median (IQR)	-2.5 (0 to -5)	-5.0 (0 to -10)
Preoperative extension deficit ≤15^0 N (%)	26 (11)	37 (16)
Flexion angle ^{0} median (IQR)	110 (100 to 120)	110 (100 to 120)
Perioperative variables		
CS fibrin sealant use N (%)	1 (0.4)	211 (92)
Surgical time minutes (IQR)	75 (60 to 100)	76 (62 to 97)
Length of hospital stay days (IQR)	4 (3-4)	4 (3-4)
Drain system used N (%)	87 (38)	79 (34)
Drain production mL (IQR)	477 (312 to 730)	550 (325 to 760)
RBC transfusions N (%)	11 (4.7)	8 (3.4)
Cemented implant N (%)	200 (85)	197 (85)

N, number; SD, standard deviation; IQR, interquartile range; ASA, American Society of Anesthesiologists score; OA, osteoarthritis; RBC, Red Blood Cells.

Patient Characteristics

Table 6.1 shows pre-and perioperative characteristics of randomized patients. The only difference at baseline was a higher incidence of diabetes in the control arm.

Primary outcome

The results of the intention-to-treat (ITT)-analysis mean change in postoperative knee extension (cExt) for patients randomized for standard care and CS after 2 weeks are shown in table 6.2. The overall mean cExt at short term follow-up was comparable between CS (crude model: CS 2.0^{o} (95%CI 1.6^{o} to 2.5^{o}) and standard care 1.8^{o} (95% CI 1.4^{o} to 2.3^{o}); mean difference of 0.2^{o} (95%CI -0.5 to 0.9). Both arms were comparable after adjusting for diabetes (model 1). Also there was no interaction between drain usage and CS (model 2).

Table 6.2: Primary outcome, cExt, two weeks after TKR

		Mean cExt (95%-CI)
Model 1		
(adjusted for DM)	Standard care	1.2 (0.5 to 1.8)
	CS fibrin	1.0 (0.3 to 1.6)
Model 2		
(adjusted for drain)		
Drain +	Standard care	0.9 (0.1 to 1.7)
	CS fibrin	1.7 (0.7 to 2.6)
Drain -	Standard care	1.3 (0.6 to 2.1)
	CS fibrin	0.6 (-0.2 to 1.3)

cExt: mean change in extension, TKR: total knee replacement, 95%-CI: 95% confidence interval, DM: diabetes mellitus, CS: CryoSeal

Secondary outcomes

Both study arms showed equal improvement in cExt at 6 weeks compared to 2 weeks (Appendix table A). There was no difference in change in knee flexion in CS patients compared to standard care. Also there was no difference in length of hospital stay between both groups (median 4 days, IQR 3-4). The Knee Society

scores significantly improved after surgery, and comparing these scores between the groups did not yield a difference (Appendix Table B). The EQ5D VAS was also similar for both treatment groups. All subscales of the KOOS improved after the surgery, there were no differences between both groups (Appendix Figure A)

Complications

Postoperative (serious) adverse events were scored up to one year postoperatively. Table 6.3 shows the complications per treatment arm. Complication rates were low and similar for the two intervention arms.

Table 6.3: Complications

	Standard care	CS fibrin
Wound infection	5 (2.1)	8 (3.4)
Deep infection	1 (0.4)	3 (1.3)
Manipulation knee (OR)	3 (1.3)	0 (0)
Manipulation knee (ward)	3 (1.3)	1 (0.4)
Knee hematoma	1 (0.4)	4 (1.7)
Pneumonia	1 (0.4)	2 (0.9)
Urinary tract infection	4 (1.7)	3 (1.3)
Admission ICU	1 (0.4)	2 (0.9)
Cardial events	10 (4.2)	6 (2.6)
Respiratory events	4 (1.7)	1 (0.4)
Neurologic events	0 (0)	3 (1.3)

Complications are reported as number (between brackets is percentage of total of treatment group)

Discussion

Topical application of a fibrin sealant (CS) did not improve postoperative knee extension at short-term (2 weeks) follow-up after TKR compared to standard care. For this study a difference in extension angle of 10^{o} improvement or more was defined as clinically relevant.[18] However, this pre-defined clinical relevant knee extension appeared not feasible as in our cohort the median preoperative extension

deficit was only 5° (IQR 0° to 10°). Nonetheless the study results also accentuate that despite extensive surgery to a knee (TKR) which creates large bleeding surfaces, the intra-articular blood loss does not seem to interfere with short-term range of motion.

Two meta-analyses studied the effect of fibrin sealant in TKR surgery, both showing a reduction of postoperative blood loss in the fibrin sealant group with a subsequent decrease in postoperative drainage and red blood cell transfusion rates.[2,14] Both found no difference in complication rate between fibrin sealant and control groups. In contrast to our study Wang et al. showed in meta-analysis a significantly improved overall mean range of motion (i.e. flexion to extension) of 16° in patients (N=144) treated with a fibrin sealant compared to those who were not treated with fibrin.[14] However this pooled mean was based on a small number of patients from only 2 studies with significant heterogeneity.

Preventing blood loss perioperatively may include numerous strategies. Intraoperative strategies could include administration of pharmacological agents, i.e. tranexamic acid application, but also topical hemostats such as fibrin sealants.[3,6]

Since generic measures for patient blood management have reduced blood transfusion considerably, focus within blood management has also shifted towards improvement of quality of life and functionality of the patient.[4] Therefore we addressed the surgical bleeding area, since this has impact on early ambulation as well as knee mobility of the surgically treated joint.

An analysis of functional outcome as primary outcome (i.e. knee extension) has not been investigated in the context of patient blood management. Knee extension deficit was used as a primary outcome since ambulating with a flexed knee is more strenuous for the patient with subsequent more energy consumption in the postoperative period. A recent small study (N=48 knees) described the effect of fibrin sealant on blood loss and, for the first time in the literature, on early functional recovery defined by knee swelling, pain, range of motion and strength of knee extension.[12] Twenty-four patients receiving bilateral simultaneous TKR were analyzed with neither any benefit of fibrin sealant in this small patient sample. Another recent study evaluated the effect of topical application of fibrinogen in TKR in 200 patients, showing no difference in terms of blood loss or transfusion frequency.[19]

Small studies have been performed assessing the optimal dosage of fibrin sealant in TKR; 2 mL is considered too little while 5 mL was considered enough compared to 10 mL in a TKR study.[20,21]

We studied a large sample of TKR patients in a prospective randomized controlled trial, with the passive extension deficit of the knee as functional endpoint. This is the first RCT with sufficient power to measure a putative effect of fibrin sealant on functional recovery of the knee. We advocate, since patient blood management is well implemented in current clinical practice in the Netherlands, that knee extension is a clinically more relevant outcome measure than transfusion rates and hemoglobin loss. Transfusion rates in the Netherlands were already low, being 11% in a total of 2.500 TKR and total hip replacement patients study on patient blood management in 2010.[4,22] These have dropped even further to 4% in the current TKR study.

A limitation of our study is that we used standard care as control and also standard care with respect to the center's preference to the use of a postoperative drain. It was considered that interference of the clinical practice during the study period (use or non-use of drain system) would cause a larger bias than just accept center wide use or no use of a drain. The study protocol allowed several factors to the preference per center (i.e. not individual preference). Another limitation is that measurements of knee angle were performed using goniometry, which is considered to be imprecise. However, due to the large number of patients included, the randomized design and blinded analysis of the study data, even the small mean change in postoperative extension in outcomes could very well be clinically interpretable even more since inter-observer variability of range of motion measurements using a goniometer show good reliability in literature.[23]

Conclusion

This study demonstrated no beneficial effects or side effects of CS fibrin sealant on the functional postoperative recovery after total knee replacement surgery. There was no difference in change of knee extension after TKR between patient treated with topical fibrin sealant or with standard care. There was also no difference between these groups in change of other postoperative outcomes. These results discourage the clinical use of a fibrin sealant after TKR.

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Appendix Table A: Mean change in knee extension compared to the preoperative extension after 2 and 6 weeks in both drain and non-drain users

Model		Mean change extension angle (95% CI)		
		Overall (up to 6 weeks)	at 2 weeks	at 6 weeks
Crude model	Standard Care	2.0 (1.6 to 2.5)		
	CS	1.8 (1.4 to 2.3)		
Model 1	Standard Care	1.7 (1.2 to 2.3)	1.2 (0.5 to 1.8)	2.3 (1.7 to 2.8)
(adjusted for diabetes)	CS	1.5 (0.9 to 2.1)	1.0 (0.3 to 1.6)	2.1 (1.4 to 2.6)
Model 2				
(usage of drain)				
Drain +	Standard Care	1.5 (0.7 to 2.3)	0.9 (0.1 to 1.7)	2.0 (1.2 to 2.8)
	CS	2.2 (1.3 to 3.1)	1.7 (0.7 to 2.6)	2.8 (1.9 to 3.6)
Drain -	Standard Care	1.9 (1.2 to 2.6)	1.3 (0.6 to 2.1)	2.4 (1.7 to 3.1)
	CS	1.1 (0.5 to 1.8)	0.6 (-0.2 to 1.3)	1.7 (1.0 to 2.4)

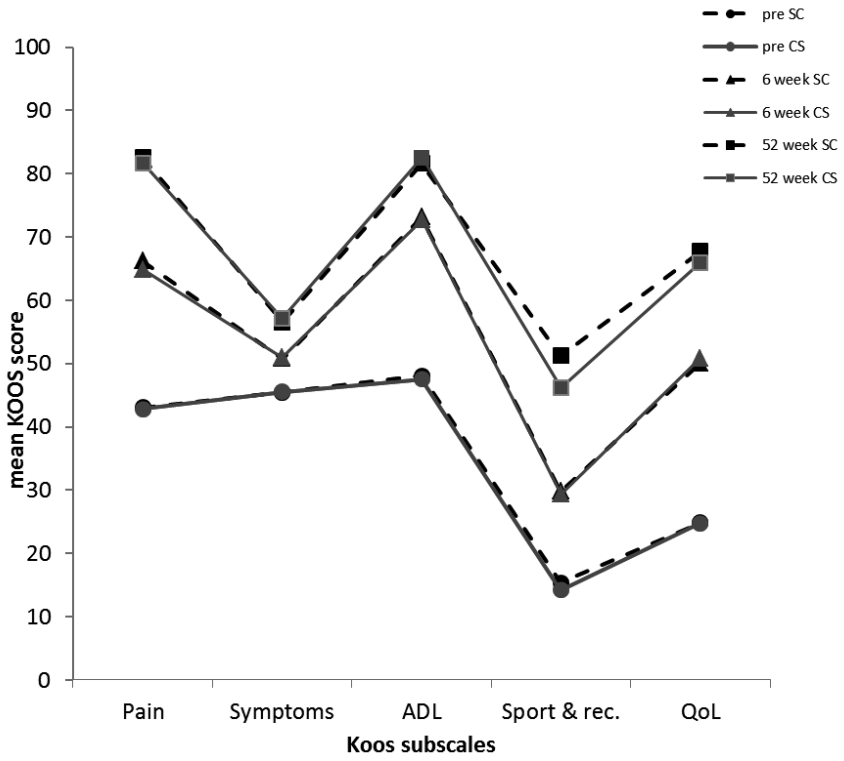
Data shown as mean cExt. angle (95%CI). Overall (up to 6 wk) and 2 and 6 week change in knee extension angle are shown as crude, adjusted (Model 1) and interaction between the drain and randomized groups (Model 2).

Appendix Table B: Knee Society Scores: Knee and Functional score

Knee Society Score	Pre		6 weeks		52 weeks	
	Standard	CS	Standard	CS	Standard	CS
Knee Score	51 (17)	51 (17)	80 (17)	78 (17)	92 (10)	90 (14)
Functional Score	47 (21)	46 (19)	59 (23)	56 (22)	77 (23)	76 (25)

Data shown as mean (standard deviation). CS, CryoSeal

Appendix Figure A: KOOS subscales preoperative and throughout follow-up



SC= Standard Care; CS= CryoSeal; ADL = activity and daily life; QoL = quality of life

Appendix <u>Transfusion protocol</u>

Patients younger than 60 years

Within 4 hours after surgery	More than 4 hours after surgery
Hb ≥ 4.0 mmol / l = 0 packed cell	Hb ≥ 4.0 mmol / l = 0 packed cell
3.0 - < 4.0 = 1 packed cell	3.5 - < 4.0 = 1 packed cell
< 3.0 = 2 packed cells	< 3.5 = 2 packed cells

Patients older than 60 years

Within 4 hours after surgery	More than 4 hours after surgery
Hb ≥ 4.5 mmol / l = 0 packed cell	Hb ≥ 5.0 mmol / l = 0 packed cell
4.0 - < 4.5 = 1 packed cell	4.5 - < 5.0 = 1 packed cell
< 4.0 = 2 packed cells	< 4.5 = 2 packed cells

Patients with increased risk (because of co-morbidity)

Within 4 hours after surgery	More than 4 hours after surgery
Hb ≥ 5.5 mmol / l = 0 packed cell	Hb ≥ 6.0 mmol / l = 0 packed cell
5.0 - < 5.5 = 1 packed cell	5.5 - < 6.0 = 1 packed cell
4.5 - < 5.0 = 2 packed cells	5.0 - < 5.5 = 2 packed cells
< 4.5 = 3 packed cells	< 5.0 = 3 packed cells

In all cases these are transfusion guidelines, of which the clinical presentation of the patient is of greater importance to which transfusion policy is followed.