Effect of Fibrin Sealant on Knee Function Restoration Following Total Knee Replacement: A Meta-analysis

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Abstract

Objective: The aim of present study was to evaluate the efficacy and safety of fibrin sealant on knee function restoration following total knee replacement.

Methods: PubMed, Web of Science, Cochrane library, and Embase were searched up to August 2021. All prospective randomized controlled trial involving fibrin sealant treatment for total knee replacement were included in this meta-analysis. Range of motion, total blood loss, blood transfusion rate, hemoglobin reduction, hospital stay, and complication were calculated using RevMan 5.4 software.

Results: Totally 23 randomized clinical trials involving 2267 patients (1136 patients for fibrin sealant group and 1131 patients for control group) were finally included. The results indicated that that the usage of fibrin sealant in total knee replacement can reduce the total blood loss [95% (-935.81, -351.70), $P < 0.0001$], transfusion rate [95%CI (0.47, 0.90), $P = 0.01$], hemoglobin reduction [95%CI (-2.94, -0.74), $P = 0.001$] and hospital stay [95%CI (-1.76, -0.42), $P = 0.001$] without increasing the rate of complication [95%CI (-0.04, 0.02), $P = 0.42$], but cannot increase the knee range of motion [95%CI (-1.17, 9.29), $P = 0.13$].

Conclusion: The usage of fibrin sealant can effectively reduce the total blood loss, transfusion rate, hemoglobin reduction and hospital stay without increasing the rate of complication, but cannot increase the knee range of motion

Introduction

As the population aged, total knee replacement (TKR) procedures performed for the treatment of knee arthritis has increased recently. By 2030, the demand for primary total knee arthroplasties is projected to grow to 3.48 million procedures in United States.[1] Furthermore, TKR is increasingly performed in two-day or even one-day surgery, requiring immediate postoperative full ambulation.[2] Thus, in addition to a satisfactory intra-operation blood loss control, a rapid knee function recovery become much more important for patients undergoing total knee replacement. Previous studies have focused on blood loss and reported significant postoperative blood loss range from 1200ml to 1800ml or even higher due to hidden blood loss.[3] Although a tourniquet is always used during operation, studies showed tourniquet application could not reduce the blood loss but increase the incidence of postoperative deep venous thrombosis and aggravate postoperative pain and swelling.[4, 5] What's more, as a key indicator for knee function, knee range of motion might be limited due to post-operation scar or tissue adhesion after total knee replacement, leading to persistent knee pain, patient dissatisfaction and even revision. A full range of motion (ROM) recovery is usually an indicator for patient discharge.

Fibrin sealant (FS), comprised mostly of fibrinogen and human thrombin, can initiate the last phase of physiological blood coagulation and reduce postoperative blood loss theoretically.[6] Over the past decades, although fibrin sealant has been widely used in surgical procedures, the effects of fibrin sealant on knee surgery remain controversial. On the one hand, some studies reported successfully reduced blood loss, along with lower blood transfusion rate and blood transfusion unit by using fibrin sealant in total knee replacement while other studies against it.[7-11] On the other hand, blood transfusion rate used to be a great concern before modern transfusion trigger protocols were introduced. However, blood transfusion rate has decreased tremendously nowadays and is no longer a major concern after total knee replacement.[12] Moreover, with the concept of Enhanced Recovery After Surgery, outcomes related to knee function and recovery speed are increasingly considered important, demonstrating a focus shift of the fibrin sealant.

Recently, several randomized controlled trials (RCTs) reported the effect of fibrin sealant on knee functions after total knee replacement published, while there is no consensus achieved. Thus, we perform this meta-analysis to further identify the efficacy of fibrin sealant on TKR. The purpose of this meta-analysis was to determine the effect of fibrin sealant on knee function restoration after total knee replacement in terms of total blood loss, hemoglobin reduction, blood transfusion rate, hospital stay, complications and most importantly knee range of motion.

Materials And Methods

This study was performed according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines.

Search strategy

PubMed, Web of Science, Cochrane library, and Embase were searched up to August 2021 by two reviewers for prospective randomized controlled trial involving fibrin sealant treatment for total knee replacement. To maximize the search specificity and sensitivity, the search algorithm was generated by different combination of keywords including: fibrin sealant, fibrin tissue adhesive, fibrin glue, total knee replacement, total knee arthroplasty, TKR, TKA and their corresponding medical subject heading (MeSH) terms. There is no language restriction on the language of the publication. All articles were imported into Endnote and reviewed to identify any omitted studies. The result of search strategy was presented in Figure 1.

Inclusion and exclusion criteria

Studies met the following inclusion criteria were included. (1) randomized controlled trials. (2) the only intervention considered was the use of fibrin sealant versus no fibrin sealant or placebo or standard care. Other interventions including drugs and functional recovery training, were permitted only when comparable of the interested intervention. (3) the main outcomes including: knee range of motion, total blood loss, blood transfusion rate. The secondary outcomes including hemoglobin reduction, hospital stay, and complications. All kinds of complications were included including fever, hematomas, thrombosis and arthropathy. Studies were excluded according to following criteria: (1) observational studies, retrospective studies, cohort studies, case-control studies, review, or case series or reports. (2) irrelevant studies. (3) the quality of studies was too low or outcome information was insufficient. Any disagreements were resolved by discussion or with a senior reviewer.

Data extraction and quality assessment

The quality of the eligible studies was independently assessed by two reviewers. The risk of bias was assessed by Review Manager 5.4.1 based on the Cochrane Handbook for Systematic Reviews of Interventions. Disagreements were resolved by consensus after discussion or a senior reviewer if necessary.

For all included studies, standard extraction form was used for both reviewers to extract data in duplicate including basic characteristics (publish year, first author, and country), patient information (age, sex, and other baseline characteristics), intervention and outcomes. Nonnumeric data were extracted by manual measurements of the published figures. The measurement data were converted to mean $\pm$ SD according to the Cochrane Handbook.

Statistical analysis

RevMan 5.4 was used for statistical analysis. Heterogeneity was evaluated by Chi^2 test, results over than 50% was considered significant and a random-effects model was applied in this case. A fixed-effects model was used when the I^2 was less than 50%. Only randomized controlled trials were included in this study and risk ratio (RR) was used for dichotomous data effect size with mean differences (MD) used for continuous data. Subgroup meta-analysis and sensitivity analysis were performed accordingly.

Results

Flow diagram of trial selection

Figure 1 presented the detailed steps of our literature search. At first, a total of 675 of records were identified through database searching and 21 of additional records were identified through other sources. After duplicates removed, there are totally 599 of records screened and 563 of records were excluded after reading the titles and abstracts. 36 of records left were assessed for eligibility by full-text. Any researches other than RCT were excluded. Researches lack intact data were also excluded. Finally, 23 RCT studies fully met the inclusion criteria were included enrolling a total of 2267 participants. Of these, eight studies reported knee range of motion data with different time points, each time points were deemed as independent trails. Notarnicola's study reported two different doses of fibrin sealant and each dose was considered as an independent trail. In general, there were 1136 patients in the fibrin sealant group and 1131 patients in the control group. The characteristics of studies included were summarized in Table 1. The risk of bias summary was presented by Figure 2 and Figure 3.

Table 1
Characteristics of the included studies

Study (Year)	Country	Cases (FS/Co)	Mean Age (FS/Co)	Male/Female (Fs)	Male/Female (Co)	BMI (FS/Co)	Doses	Origin of FS	Operation methods	Drainage
Aguilera 2013	Spain	43/43	72.6/74.9	7/36	7/36	30.1/29.8	4-8ml	Product fibrin glue	Primary TKR	Yes
Bae 2014	Korea	50/50	68.8/69	4/46	8/42	26.41/24.81	5ml	Floseal	Unilateral TKR	Yes
Bloomfield 2012	America	50/50	66.3/62.4	22/28	21/29	33.9/33.4	10ml	Autologous PRP with thrombin	Primary unilateral TKR	No
Di Francesco 2013	Italy	51/42	67.9/70.2	24/27	17/24	26.5/26.2	10ml	Floseal	Unilateral TKR	Yes
Hesse 2014	USA	100/100	66.33/67.85	NS	NS	31.91/30.82	10ml	Evicel	Unilateral TKR	Yes
Horstmann 2011	Netherland	20/20	67/66	14/6	13/7	NS	11ml	Autologous PRP	TKR	Yes
Kim 2012	America	97/99	NS	NS	NS	NS	10ml	Floseal	Primary TKR	Yes
Kluba 2012	Germany	12/12	70.8/71	6/6	4/8	NS	2ml	Quixil	Bilateral TKR	Yes
Levy 1999	Isreal	29/29	68.9/70.2	23/6	23/6	29.8/29.1	10-20ml	Quixil	Unilateral TKR	Yes
McConnell 2012	UK	21/22	NS	NS	NS	31.5/30	10ml	NS	TKR	Yes
Molloy 2007	England	50/50	NS	NS	NS	29.31/28.03	10ml	Product	Primary TKR	NS
Morishita 2014	Japan	20/20	72/74.7	2/18	0/20	26.5/25.4	10ml	Autologous PRP	Unilateral TKR	No
Pavao 2019	Spain	32/31	69.19/69.48	4/28	5/26	31.81/31.23	6ml	Evicel	Primary TKR	NS
Randelli 2014	Italy	31/31	69/71	26/31	22/31	28/29	5ml	Evicel	Primary TKR	Yes
Romanò 2015	Italy	24/24	71.7/71.2	7/17	8/16	NS	12ml	Floseal	Primary TKR	No
Sabatini 2012	Italy	35/35	70.7/70.4	10/25	6/29	NS	10ml	Quixil	TKR	Yes
Skovgaard 2013	Denmark	24/24	65/65	11/13	11/13	28/28	10ml	Evicel	Bilateral TKR	Yes
Suarez 2014	America	54/54	65.9/65.1	20/36	21/31	29.8/33.7	10ml	Product	Primary TKR	Yes
Tandogan 2021	Turkey	40/40	68/70	5/35	4/36	30.77/31.39	5ml	Autologous PRP	Primary TKR	Yes
Vera 2018	Netherland	234/232	68/68	82/152	86/148	29/29	10ml	Cryoseal	Primary TKR	No
Wang 2001	America	25/28	NS	NS	NS	NS	10ml	Quixil	Unilateral TKR	Yes
Yan 2021	China	34/35	69.71/6.79	6/28	3/32	29.38/28.59	10ml	Floseal	TKR	Yes
Notarnicola 2012 (5ml)	Italy	30/30	NS	19/41	19/41	NS	5ml	Quixil	TKR	Yes
Notarnicola 2012(10ml)	Italy	30/30	NS	21/39	21/39	NS	10ml	Quixil	TKR	Yes
Abbreviation: BMI, Body mass index; Fs, Fibrin sealant; Co, Control; NS, not stated.										

Quality assessment

The Cochrane Handbook for Systematic Reviews of Interventions was used to evaluate the risk of bias for all eligible studies by two independent reviewers. The results presented in Figure 2 and Figure 3. For all studies, one study was high risk on blinding of participants and personnel (performance bias). And there were two studies with high risk on blinding of outcome assessment (detection bias). Totally, the results of quality assessment indicated a small overall bias and relatively high quality.

Effects on knee range of motion

A total of eight studies reported data on knee range of motion using different time points [13-20], lacking consistency and comparability. Thus, a subgroup analysis was performed with four time intervals: 0 days - 3 days, 3 days - 1 week, 1 week - 1 months, 1 months - 3 months, each time points of articles were deemed as independent trails. Notarnicola's study reported two doses of fibrin sealant and each dose was considered as an independent trail. Random-effects model was used for large heterogeneity ($I^2=93\%$). The results showed significant difference between fibrin sealant group and control group during at 3 days to 1 month [95%CI (2.50, 22.42); $p=0.01$]. No statistical difference was found at the other time intervals as well as in total [95%CI (-1.17, 9.29), $P=0.13$] (Figure 4).

Effects on total blood loss

A total of 21 studies reported intact data related to blood loss [15-36]. Among these studies, 6 studies solely reported intact data on drain-out blood loss [16, 17, 19, 21, 25, 37] and 11 studies solely reported intact data on total blood loss [18, 20, 23, 26-36, 38], while 4 studies reported intact data on both drain-out blood loss and total blood loss [23, 26, 33, 35]. Thus, we performed a subgroup analysis for drain-out blood loss and total blood loss. Random-effects model was used in both subgroup analysis due to significant heterogeneity. Results showed that fibrin sealant significantly reduced drain-out blood loss compared to control group [95%CI (-2383.37, -376.45), $P=0.007$] while failed to reach statistical significance in total blood loss reduction [95%CI (-249.53, 37.28), $P=0.15$] (Figure 5). Totally, the usage of fibrin sealant reduced total blood loss [95% (-935.81, -351.70), $P<0.0001$].

Effects on blood transfusion rate

Totally 16 studies provided data on blood transfusion rate and the results indicated significant heterogeneity ($I^2 = 56\%$, $P = 0.003$) [15, 17-20, 23, 25, 26, 28, 30, 32, 34-36, 38, 39]. Random-effects model was applied and results showed that fibrin sealant administration reduced the blood transfusion rate compared with the control group [95%CI (0.47, 0.90), $P=0.01$] (Figure 6). Fibrin sealant might reduce the transfusion rate of total knee replacement.

Effects on hemoglobin reduction

Based on the inclusion criteria, a total of 9 studies providing data of hemoglobin reduction were included in this study (Figure 7) [15, 17, 23, 25, 26, 30, 34, 35, 39]. Significant difference between fibrin sealant group and control group was observed [95%CI (-2.94, -0.74), $P=0.001$].

Effects on hospital stay

Eight eligible studies reported the time of hospital stay [17-19, 21, 23, 26, 33, 35]. Analysis of these studies revealed statistically significant difference between the fibrin sealant group and control group indicating using fibrin sealant may reduce the time of hospital stay [95%CI (-1.76, -0.42), $P=0.001$] (Figure 8).

Effects on complication

Seventeen studies reported intact data of complication including fever, hematoma, thrombosis, and arthropathy [12, 15, 17-21, 25-27, 29, 30, 32, 34, 36, 38, 39]. The analysis of these studies exhibited no significant difference between the fibrin sealant group and the control group, demonstrating using fibrin sealant may not interfere the rate of complication [95%CI (-0.04, 0.02), $P=0.42$].

Sensitivity Analysis

To enhance the credibility and determine the origin of heterogeneity, we conducted sensitivity analysis by removing each study at a time and recalculating the meta-analysis for the remaining studies, results showed a similar trend which confirmed stability of our analysis of range of motion, total blood loss, hemoglobin reduction, transfusion rate, hospital stay, and complication.

Discussion

The present meta-analysis indicated that the usage of fibrin sealant in total knee replacement may reduce the total blood loss, transfusion rate, hemoglobin reduction and hospital stay, but the effect of knee range of motion and complication was not significant. In this study, only randomized controlled trials were included, resulting in 23 studies for the meta-analysis.

Most studies used 10ml as the dosage of fibrin sealant and both unilateral and bilateral total knee replacement were included. Although fibrin sealant has been used in surgical procedures for decades, the effects of fibrin sealant on total knee replacement still lack consensus. Previous studies mostly focused on hemostasis effect of fibrin sealant and topics related to blood loss, including total blood loss, hemoglobin reduction and blood transfusion [10, 40]. However, as the requirement of rapid recovery increased, reducing hospital stay and promoting functional restoration become much more urgent. Knee range of motion, the key indicator of discharge and knee functional recovery, is very important but usually forgotten or underestimated in the precious studies [3, 10, 40]. We aimed to evaluate the effect of fibrin sealant on enhanced recovery after surgery (ERAS) of total knee replacement and focused on the knee range of motion and hemostasis as well.

The group treated with fibrin sealant had a lower total blood loss, transfusion rate, and hemoglobin reduction indicating the usage of fibrin sealant is helpful in blood loss control. Although recently published RCTs reported no effect of fibrin sealant on blood loss after total knee replacement. Our research still supported the usage of fibrin sealant on total knee replacement for hemostasis. We assume the reasons may be the different types of fibrin sealant used. As presented in Table 1, forseal, Evicel and Quixil were three most common fibrin sealant used which contains tranexamic acid. However, as Randelli et al. reported, some fibrin sealants were derived from human plasma and contains only human components without tranexamic acid which is an effective hemostasis agent for fibrinolysis inhibition.

There are 8 studies provided intact data of knee range of motion [13-20], but each study used different time points set by author. For consistency, we concluded these time points into four time intervals and performed subgroup meta-analysis, each time points were referred as an independent trial. For intervals of 3 days to 1 week, results demonstrated that the usage of fibrin sealant might help the improvement of knee range of motion. However, analysis of the rest time intervals failed to reveal significant difference as well as in total. We have noticed a significant heterogeneity of 3d-1w interval and the heterogeneity of total analysis was mostly from this time interval. Thus, we performed a sensitivity analysis, results displayed a similar trend which indicated that our analysis was stable. Studies reporting intact data of range of motion always reported it with different time points which varied a lot between different trials. However, previous analysis of fibrin sealant focused mostly on hemostasis effect but paid insufficient attention to knee function restoration and were outdated [3, 10, 40]. Knee range of motion was frequently regarded as a secondary outcome and analyzed in one piece with large heterogeneity. Different from previous studies [7], we divided it into four time intervals and found a opposite result. Only in 3 days to 1 week, using fibrin sealant may help the improvement of knee range of motion. But in the other time intervals and in total, using fibrin sealant was not helpful for knee range of motion recovery. On the other hand, using fibrin sealant during total knee replacement may not hinder the knee range of motion recovery. As a derivative of fibrin, the main component of scars, fibrin sealant may exacerbate the scarring and adhesions after total knee replacement and further interfere the recovery of knee function. However, our research denied this hypothesis. What's more, our analysis also found using fibrin sealant may not increase the incidence of complications but decrease the time of hospital stay. In conclusion, using fibrin sealant was considered safe for knee function restoration.

Although standard procedures and careful assessment were performed in this meta-analysis, some potential limitations still exist: (1) differences of dose and compound of fibrin sealant may have an effect on the results. (2) clinical and statistical heterogeneity may reduce the credibility of final results.

In conclusion, patients undergoing total knee replacement would benefit from fibrin sealant with reduced total blood loss, transfusion rate, hemoglobin reduction, and hospital stay but may benefit little from knee range of motion. Our study suggested that fibrin sealant use is effective and safe. While a large and well-designed randomized controlled trial is still needed to investigate the risks and benefits of the use of fibrin sealant.

Abbreviations

Total knee replacement (TKR)

Range of motion (ROM)

Fibrin sealant (FS)

Randomized controlled trials (RCTs)

Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA)

Medical subject heading (MeSH)

Risk ratio (RR)

Mean differences (MD)

Enhanced recovery after surgery (ERAS)

Body mass index (BMI)

Control (Co)

Not stated (NS)

Declarations

Ethics approval and consent to participate:

not applicable.

Consent for publication:

All author had approved the version to be published.

Availability of data and materials:

This manuscript has no associated data or the data will not be deposited.

Competing interests:

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Authors' contributions:

All author had made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work. All author agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figures

Figure 1

The flow diagram of the selection process

Figure 2

The risk of bias summary

Figure 3

The risk of bias graph

Figure 4

Subgroup meta-analysis of knee range of motion

Figure 5

Subgroup meta-analysis of total blood loss

Figure 6

Figure 7

Effects on hemoglobin reduction

Figure 8

Effects on hospital stay

Figure 9

Effects on Complication