

# Application of Iced Normal Saline Combined with Cocktail Perfusion in Total Knee Arthroplasty: Randomized Controlled Trial

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## Research article

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# Abstract

*Background:* The present study was designed to investigate the safety and effectiveness of iced normal saline combined with cocktail perfusion during total knee arthroplasty (TKA).

*Method:* Sixty patients undergoing TKA were divided into three groups, then three different intra-operative articular cavity perfusion treatment was given according to the randomized, double-blind and controlled rule. One way ANOVA analysis on visual analogue scale (VAS) score, functional recovery, drainage, and edema of the affected limb were performed to assess the efficiency of the treatment in the following three days after the operation.

*Results:* Postoperative drainage in group A and B reduced significantly ( $P < 0.05$ ). The IHC scores of the surgical limbs were markedly lower comparing with the control group ( $P < 0.05$ ). No differential postoperative edema was observed and the patient acquired better rehabilitation in group A and B than control group. Compared with group A, no differential postoperative drainage and edema was seen in group B ( $P > 0.05$ ). The VAS score of group B was significantly lower than in group A ( $P < 0.05$ ). Postoperative recovery of the surgical limb function in group B was better than in group A ( $P < 0.05$ ), and PGE2 in the postoperative drainage volume of group B was significantly decreased ( $P < 0.05$ ).

*Conclusions:* Intra-operation articular cavity perfusion therapy with iced normal saline combined with cocktail perfusion therapy can greatly reduce the early inflammation, contributing to the better rehabilitation of TKA.

## Background:

Knee osteoarthritis (KOA) is a common disease caused by the degradation of articular cartilage, which is manifested as painful, edema, stiffness and restrained mobility of the knee. Although KOA is not fatal, it seriously reduces the life quality of the elder patients. According to the survey in the USA, females with KOA suffered higher risks than the normal, which might be correlated with the disordered mental health induced by the chronic pain and the sports barrier. Meanwhile, the morbidity of obesity and cardiovascular event increased due to the limited exercise caused by the KOA which severely impact the quality of the human life.

Early symptoms of KOA could be relieved by the conserve therapy such as health education, sports therapy and drug treatment. Clinical intervene including arthroscopic debridement and cartilage graft were also applied to retard the progression of KOA. However, advanced KOA was irreversible. Total knee arthroplasty, which was acknowledged as the most effective treatment for advanced knee osteoarthritis, was widely accepted to relieve the pain of KOA and restore the function of the knee. Nevertheless, many patients refused TKA due to the fear of the pain post-operation.

Recent year, how to alleviate postoperative pain and promote rapid recovery of patients has witnessed an increased research interest. Iced normal saline combined cocktail perfusion therapy was used in present

study to decrease the post-operative pain of the surgical limb and restore the limb function as soon as possible.

## **Methods:**

### **Objectives and inclusion criteria:**

Sixty patients undergoing unilateral total knee replacement in joint surgery of Yantai Yuhuangding Hospital from 2nd March 2018 to 1st June 2018 were included in present study. All the patients voluntarily participating in this study have understood the research project and signed the corresponding consent forms. The patients, their family members and the nursing staff were not aware of the specific grouping situation.

Patients with confirmed primary knee osteoarthritis in stage IV by preoperative X-ray were included in present study, whilst subsequent arthritis (including rheumatoid arthritis, Gouty arthritis, traumatic arthritis, etc.) were excluded. Kellgren-Lawrence Radiology standards for stage IV were listed as follows: obviously narrowed joint space; vast osteophytes are formed; severe osteosclerosis under the cartilage; bone hypertrophy and evident deformity. (Fig. 1)

### **Treatment of the patients**

Systemic preoperative inspections were performed to exclude any contraindications to surgery, and the consent forms were signed before operation.

Patients were divided into three groups according to the randomized, double-blind, and controlled method. Group A: twenty patients who were given intraoperative joint cavity infusion therapy using 20ml tranexamic and 40ml iced normal saline; Group B twenty patients who were given 20ml of iced normal saline, 20ml of iced cocktail and 20ml of tranexamic; the left twenty patients were given joint cavity infusion therapy with 20ml tranexamic only as the control group. Intravertebral anesthesia was selected for the surgery and the operations were performed by the same surgical team. The average operation time was about 1.5 hours, which lasted from the compression of the tourniquet to completed wound dressing.

Intraoperative cocktail infiltration anesthesia and adductor tube blocking therapy were performed routinely for all the patients. Posterior stable Prothesis (Nexgen-LPS, Zimmer, US) was applied for the operation (Fig. 2). Cocktail was formulated during the operation by mixing Ropivacaine 150mg, Morphine 10mg and Epinephrine 1mg, then normal saline was used to dilute the mixture to 60ml. Ropivacaine 150mg was used for the block therapy. High pressure drainage system (PFM, Germany) was applied intraoperation and the drainage tube was clamped for 6 hours after operation. The drainage tube was removed 24 hours after the operation. The first dose of anticoagulant (nadroparin calcium 4100 IU) was applied 8 hours after the operation. Tranexamic acid was also applied during the perioperative period both cavity irrigation and intravenous infusion. The first dose for intravenous infusion was performed

after loosening the tourniquet, repeated doses of tranexamic acid were given intravenously immediately when the patients were sent back to the ward and every 3 hours for 3 times. Postoperative rehabilitation training was performed routinely after the operation as soon as possible.

## Observation index

The visual analogue scale (VAS) scoring system was applied to evaluate the pain in the following 24, 48 and 72 hours after surgery. The hospital for special surgery (HSS) scores of the following three days after surgery were assessed. The 24-hour postoperative drainage volume and the limb swelling values were recorded.

Based on the analysis of subjective feelings and objective data such as the drainage, the swelling value, etc, of patients after surgery, the effect of intra-operative iced saline combined cocktail perfusion therapy was evaluated.

## Statistical analyses

Comparison between the two groups is completed by student T-test whilst one way ANOVA was used to compare the difference among the three groups.  $P < 0.05$  was regarded as statistical difference. One way ANOVA and student T-test were performed using SPSS 26. 0.

## Results:

### General conditions of patients in each group

No significant difference was observed in gender, age, pre-operative HSS scores and pre-operative joint circumferences among three groups. The samples were qualified for the requirement of homogeneity. (Table 1)

Table 1  
Comparison of the general conditions (Mean  $\pm$  SD)

	Age	HSS score	Pre-operative joint circumferences(cm)
Control group	66.55 $\pm$ 5.58	45.05 $\pm$ 3.19	46.57 $\pm$ 3.22
Group A	65.75 $\pm$ 4.77	44.65 $\pm$ 2.99	46.73 $\pm$ 3.06
Group B	65.70 $\pm$ 4.92	45.45 $\pm$ 3.08	45.82 $\pm$ 3.58

### ***Statistical analysis of postoperative observation indexes of the three groups.***

One way ANOVA was performed to compare the differences of the 24-hour postoperative drainage volume, postoperative pain score (24, 48, 72h) and HSS score on the third day after the operation among the three groups. No differential swelling value was observed at 24 hours after operation ( $P > 0.05$ ). Statistically altered postoperative drainage (24 hours after operation) and postoperative pain score (24, 48, 72h after operation) and HSS score on the third day after surgery were shown in both group A and group B, comparing with the control group (Table 2). Compared with group A, there was no significant difference in group B on HSS score at 24 hours and the third day after surgery, whilst postoperative pain scores of group B present significant difference ( $P < 0.01$ ). Details are shown in Table 2 and Fig. 3.

Table 2  
Statistical analyses of the postoperative indexes (Mean  $\pm$  SD).

	Drainage(ml)	Swelling value(cm)	Postoperative VAS scores			Postoperative HSS scores
			24h	48h	72h	
Control group	301.5 $\pm$ 37.1	1.15 $\pm$ 0.67	6.6 $\pm$ 0.96	5.15 $\pm$ 0.96	3.7 $\pm$ 0.71	56 $\pm$ 6.35
Group A	140.25 $\pm$ 34.4**	1.2 $\pm$ 0.53	5.05 $\pm$ 0.74**	3.50 $\pm$ 0.87**	2.45 $\pm$ 0.67**	61.25 $\pm$ 4.56**
Group B	127.5 $\pm$ 29.8**	1.10 $\pm$ 0.60	3.75 $\pm$ 0.70**	2.35 $\pm$ 0.873**	1.55 $\pm$ 0.59**	61.85 $\pm$ 3.47**

Note: \*\*  $P < 0.01$

## Postoperative complications

None of the three groups had serious complications such as infection, poor incision healing, joint dislocation, and vein thrombosis event (VTE). In the control group, 5 patients were given flurbiprofen sodium intravenous pump for pain relief after the operation. No analgesia pump was applied in the experimental group A and the experimental group B; Three patients in the experimental group B suffered from nausea and vomiting after the operation. Luckily the symptoms were not serious, no special treatment was given; None of the three groups of patients received blood products after operation.

## Discussion:

As the aging of the population and the increasing requirement of the life quality of the elders, total knee arthroplasty, the most effective method to cure advanced KOA, is urging these years. However, postoperative pain and bleeding are still the head-paining issue for both the patients and the arthrologists. Satisfied pain-relieving intervene and bleeding-reduced treatment play pivotal role in acquiring an ideal rehabilitation [1].

Postoperative pain is a nightmare for patients. Studies showed that about 30% of patients suffered from moderate pain after TKA, and about 60% of patients reached severe pain [2]. According to Dorr's survey [3], only less than half of the early pain after TKA can be effectively controlled. Severe postoperative pain will exert inverse effect on the cardiovascular, endocrine, respiratory and other systems, as well as the internal environment balance, which may also trigger the psychological disorders, such as anxious or insomnia after the operation. In particular, the pain will induce the muscular tension of the knee, which may bring out the resistance for early activity and functional exercise, leading to the unsatisfied rehabilitation. Reuben et al. [4] also believe that uncontrolled early pain after TKA is one of the main causes of postoperative chronic pain.

The pain after TKA is mainly manifested as moderate to severe pain, which is caused by the mechanical damage of surgical dissection. As the constant stimulation of massive pain mediator, lower pain threshold is accumulated for the peripheral nerve pain receptors, meanwhile the stimulation is conducted through nerves to the central nervous system which prolonged the central response time, leading to the increased intensity and eventually a hypersensitivity response.

Effective postoperative analgesia not only alleviate the patient's subjective feelings of pain, but also reduce post-operative complications such as deep vein thrombosis and pulmonary embolism in the lower limbs caused by lack of exercise. Research revealed that timely active exercise is the most effective method to prevent the adverse thrombosis event, nevertheless, the prerequisite for effective functional exercise after surgery is to obtain the satisfied analgesia. What's more, early active exercise is essential for the recovery of knee function [5]. In addition, the post-operative pain is also closely correlated with patients' age, gender, type of operation, and operation time. No statistical difference is observed in the listed influencing factors in present study.

Massive bleeding, including obvious bleeding and invisible bleeding, often occurs after TKA. Bleeding is highly correlated with gender, coagulation function, intraoperative application of tourniquet, prosthesis design, surgical technique, and the use of hemostatic drugs [6]. Obvious bleeding is mainly reflected in the postoperative drainage, whilst postoperative swelling of the soft tissue around the knee joint is the main reflection of invisible bleeding. According to Pattison's [7] research, invisible bleeding is mainly caused by hemolysis and bleeding into the soft tissue space. Excessive bleeding after surgery often results in a reduced hemoglobin, which leads to anemia and delays early rehabilitation. Anemia can be corrected by allogeneic blood transfusion in a short time, however, many complications of the blood transfusion, such as the transmission of infectious diseases, side effect of blood transfusion and immunosuppression may follow [8]. Meanwhile, the shortage of blood reserves in recent years has made it more and more difficult to transfuse allogeneic blood. Therefore, effective methods to reduce peri-operative pain and postoperative bleeding is essential. Intraoperative joint perfusion with iced normal saline and cocktail is undoubtedly a simple and easily performed method.

Nowadays, cold compress therapy is employed to treat various acute injuries [9, 10]. Cold compress can dispel the inflammation mediators by constricting capillaries to intercept the progression of

inflammation, contributing to the hemostatic and analgesic effects. Research in acute soft tissue injury revealed that pressurized cold compress treatment can significantly slow down the speed of nerve conduction and reduce the sensitivity of local nerve endings to relieve the pain [11]. The present study showed that the VAS scores of patients in the ice-salt water group and ice-salt-salt-mixed cocktail group were significantly lower than those of the control group at 24, 48, and 72 hours post-operation ( $P < 0.05$ ).

Cocktail therapy in TKA has been clinically applied widely, although there is no universal criteria for the recipe. We modified the cocktail recipe basing on the consensus of experts. In addition to ropivacaine and epinephrine, morphine and triamcinolone acetonide were also formulated and diluted with normal saline to 60ml. Intraoperative extensive injection of cocktails could directly block the signalling transduction of vast pain receptors in the knee joint cavity to achieve a good analgesic effect [12]. Generally, ropivacaine, lidocaine and bupivacaine are used for local anesthesia. Due to the advantage of long action time, strong anesthetic intensity and small cardiovascular side effects, ropivacaine was selected in our cocktail. On the other hand, ropivacaine presents exert little effect in blocking the motor nerves, and it does not delay the early postoperative rehabilitation. Although it is a central opioid analgesic, morphine also has periphery receptors. The topical application not only presents a good analgesic effect, but also can avoid the side effect of morphine such as urine storage, lethargy, and dry stool to a certain extent. Adrenaline can constrict local blood vessels, delay the absorption and metabolism of the cocktail, and extend the action time of the cocktail.

Through clinical assessment, the analgesic effect of iced normal saline combined cocktail is much better than just using pure iced normal saline ( $P < 0.05$ ). Thus, the postoperative pain and the inflammation are significantly reduced. As a result, patients can rehabilitate earlier, contributing to the promotes the recovery of knee function. The postoperative HSS scores of patients on the third day after surgery in the iced normal saline group and the iced normal saline combined with cocktail group were markedly higher than that of the control group ( $P < 0.05$ ).

Routinely intra-operative extensive soft tissue loosening, osteotomy and patella repair in TKA lead to enlarged wounds and serious bleeding. How to reduce post-operative bleeding, reduce the incidence of blood transfusion and related postoperative complications is the special attention should be paid after TKA. Previous report showed that cold compresses after TKA proved to significantly lower pain, reduce bleeding and improve the sleep quality [13]. Iced perfusion can promote the capillary constriction to decrease the bleeding, on the other hand, the increased local pressure of the joint cavity after the perfusion of ice normal saline could compress the capillaries in the wound, thereby achieving the hemostasis.

Elastic bandage dressing was also applied in our clinical practice to reduce the leakage of the broken ends of the lymphatic vessels in the joint cavity and promote the venous blood return. Recent years, ranexamic acid is proved to exert pivotal role in controlling hyperfibrinolytic bleeding after TKA, intraoperative and postoperative application of ranexamic acid significantly reduced the incidence of blood tranfusion and the postoperative inflammation [14]. In the present study, drainage in the iced

normal saline group and the iced normal saline mixed with cocktail group was significantly lower than that in the control group at 24 hours after surgery ( $P < 0.05$ ). Considering the risks of normal saline penetrating into the soft tissue around the joints to induce the joint swelling, we measure the circumference of the thigh 10 cm above the knee after TKA. No statistical differential circumstance was observed between the joint cavity perfused and control group, which indicated that the perfusion therapy did not increase the postoperative swelling.

## **Conclusions:**

Iced normal saline combined with cocktail infusion during TKA significantly reduced the perioperative blood loss and lower postoperative pain score without increasing the swelling of the surrounding soft tissues, which tended to be a safe and effective clinical practise in TKA. However, due to the limited sample numbers and lack of long-term follow-up study, potential side effects and the more details on this method such as the individually designed perfusion pressure still need further exploration.

## **Abbreviations**

TKA: total knee arthroplasty

KOA: Knee osteoarthritis

VAS: visual analogue scale

HSS: hospital for special surgery

VTE: vein thrombosis event

## **Declarations**

### ***Ethics approval and consent to participate***

The current research was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Yuhuangding Hospital on 12 January 2018 (NO. 2018149). Written informed consent was obtained from individual or guardian participants.

### ***Consent for publication***

Not applicable.

### ***Competing interests***

The authors declare that they have no competing interests.

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## ***Author's Contributions***

Experimental design: LJS and GDW; Data collection: LJS, PZG and JWW; Data analysis: LJS, JWW, JW and GDW; Manuscript preparation: all.

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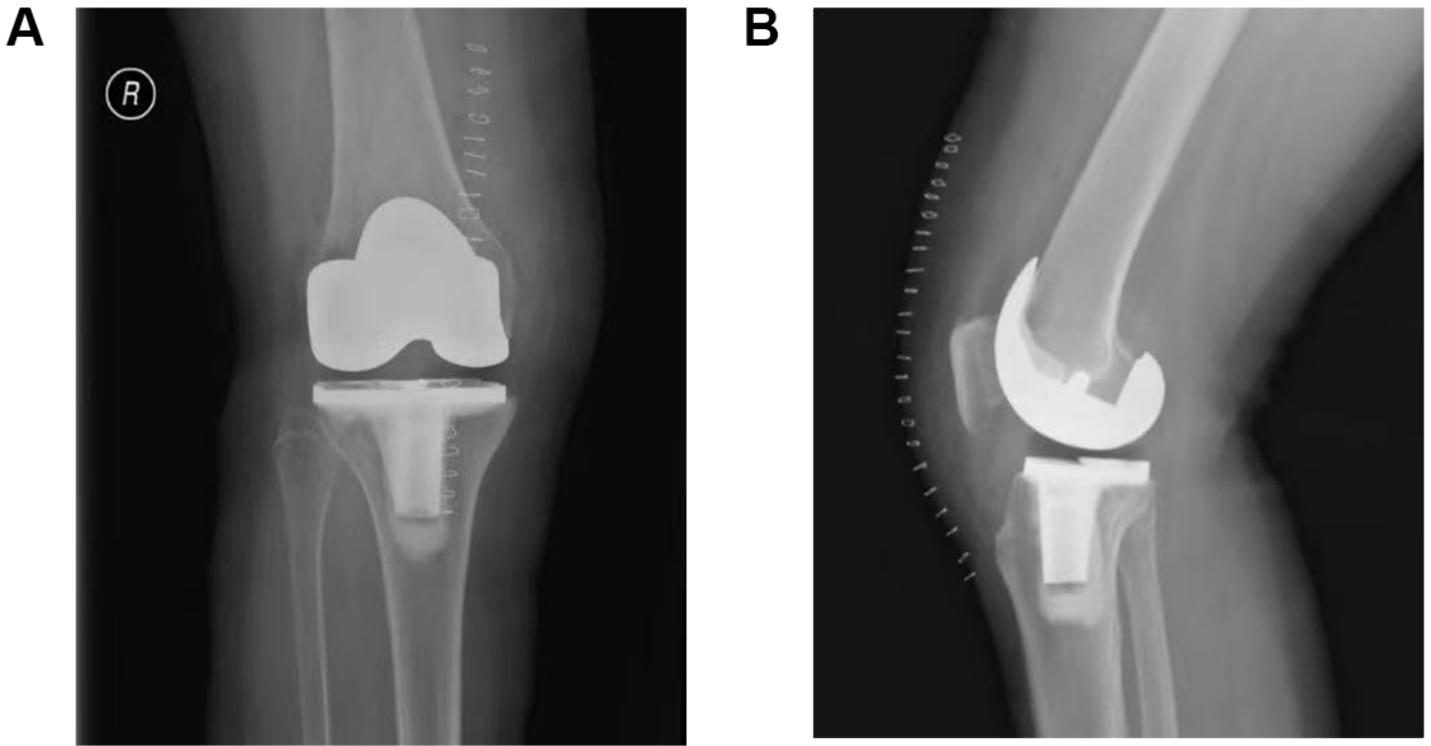
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## Figures



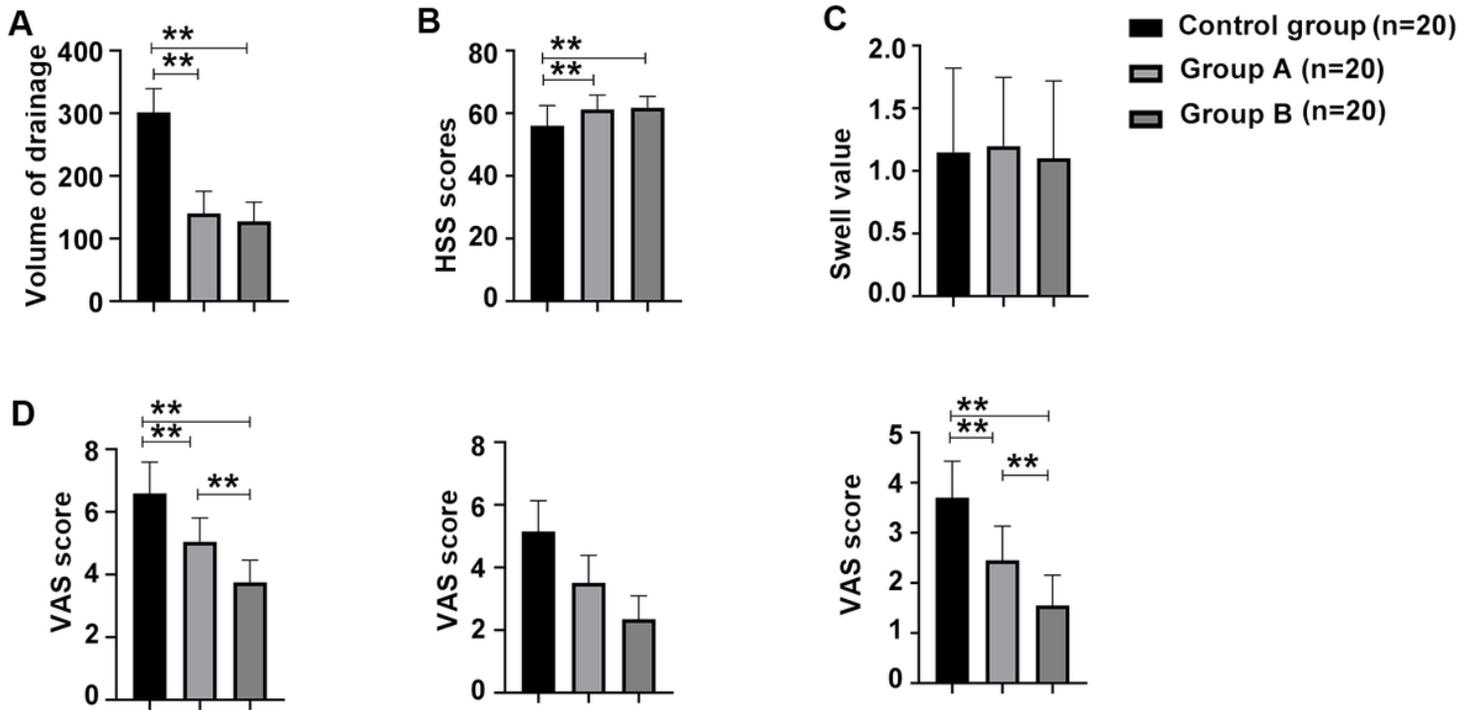
**Figure 1**

Preoperative X-ray of the knee. (A) X-ray was taken from the anterior and posterior ankle of the knee. (B) X-ray was taken from the lateral ankle of the knee.



**Figure 2**

Postoperative X-ray of the knee. (A) X-ray was taken from the anterior and posterior ankle of the knee. (B) X-ray was taken from the lateral ankle of the knee.



**Figure 3**

Altered postoperative observation indexes in three groups. (A) Histogram to present differential postoperative drainage volumes in three groups. (B) Altered postoperative HSS scores in three groups. (C) Swelling values after operation in three groups. (D) VAS scores in the groups were shown in the 24 hours, 48 hours and 72 hours after operation, respectively. \*\*  $P < 0.01$ .

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