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Review Article

Tourniquet-Induced Ischemia-Reperfusion Injury during Total Knee Arthroplasty

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ABSTRACT

Aim of review: To review the advantages and disadvantages of tourniquet use during total knee arthroplasty (TKA) and the management of tourniquet-induced ischemia-reperfusion injury.

Methods: The PubMed database was systematically searched for related literature using the following keywords: "total knee replacement" or "total knee arthroplasty", "tourniquet", and "ischemia reperfusion" or "ischemia reperfusion injury". The selected literature was then read by the authors and manually identified.

Recent findings: Tourniquet use during TKA reduces the volume of blood loss and the requirement of blood transfusion, and shortens the duration of surgery. However, it induces ischemia-reperfusion injury that provokes local as well as systemic inflammation, producing harmful effects to the involved limbs (muscle swollen and atrophy and persistent weakness) and local as well as remote organs (deep vein thrombosis, lung injury, wound complications, etc.). To decrease tourniquet-related harmful effects, the duration of ischemia should be kept as short as possible. Other measures such as providing propofol sedation or antioxidant, and performing ischemic preconditioning may be helpful to attenuate ischemia-reperfusion injury but require further demonstration.

Conclusion: Tourniquet use during TKA has both advantages and disadvantages. Tourniquet-induced ischemia-reperfusion injury is a major source of harmful effects. The benefits and risks of the tourniquet use should be carefully evaluated before making the decision.

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Over 719,000 total knee arthroplasties (TKAs) were performed in 2010 in the United States (1) and the number is expected to exceed 3.4 million annually by 2030 (2). Although no exact data are reported in Chinese patients, a similar trend can be expected as a result of aging population. TKA effectively mitigates the chronic pain associated with osteoarthritis and restores functional mobility for many elderly patients (3). Tourniquet is frequently used during TKA to decrease intraoperative blood loss and transfusion, and to improve visualization of structures as well as fixation of cementation by providing a relatively bloodless operating field (4-7). On the other hand, tourniquet use during TKA provokes ischemia-reperfusion (IR) injury in lower-limb skeletal muscles (8) and local as well as systemic inflammation (9-11). The reported postoperative complications associated with tourniquet use include reduced motion range (12, 13), increased limb swelling (14, 15), elevated pain severity (14, 16-17), occurrence of wound compli-

cations (18, 19), more frequent cardiac and cerebral microemboli (20, 21), and development of deep venous thrombosis (6, 16, 22) and peripheral nerve injury (7). Therefore, the benefit-risk ratio of tourniquet use during TKA should be carefully balanced.

This review aims to evaluate the advantages and disadvantages of tourniquet use during TKA and the management of tourniquet-induced IR injury.

The PubMed database was systematically searched to obtain the related literature in the English language by combining the free text and MeSH thesaurus terms: "total knee replacement" or "total knee arthroplasty", "tourniquet", and "ischemia reperfusion" or "ischemia-reperfusion injury". The selected literature was then read and identified by the authors. Additional literature was manually screened from the references of identified literature.

Why Use Tourniquet During TKA?

Like other orthopedic surgeries, TKA is frequently associated with a significant amount of blood loss and a requirement of blood transfusion (23). Pneumatic tourniquets which have been used since almost a century ago can provide a blood-free operating field and a clear visualization of structures, reduce intraoperative bleeding, and improve fixation of cementation through occluding the blood flow. In order to use tourniquet safely for lower extremities, the widest possible cuff should be chosen, the tourniquet size should be half of the limb diameter, the tourniquet pressure should be 100 mm Hg above the patient's systolic blood pressure, and the inflation time should be less than 90 minutes (24). For patients in whom the tourniquet must be used longer than the safe time limit, try to split the ischemic period by a short interval (10-15 minutes) of tourniquet deflation (24, 25).

Systematic reviews confirmed the effects of tourniquet use during TKA. A recent systematic review conducted by Jiang et al. (26) included 26 randomized controlled trials (RCTs) that were conducted from 1966 to 2013, involved 1, 450 knees and compared the clinical outcomes after TKA with or without tourniquet use. Pooled results showed that the use of tourniquet reduces the volume of intraoperative blood loss, decreases the requirement of blood transfusion, and shortens the duration of surgery; however, it does not reduce postoperative blood loss and total blood loss when compared with surgery without tourniquet use. Similar conclusions were also achieved by others (16, 27-28). The 2015 guideline from American Academy of Orthopedic Surgeons (AAOS) provided moderate recommendation for the use of tourniquet during TKA to decrease intraoperative blood loss (29). However, lower-limb ischemia-reperfusion injury remains a great concern when using this technique.

Ischemia-Reperfusion Injury Induced By Tourniquet

Pathophysiologic Changes

With inflation and deflation of tourniquet, lower-limb tissues undergo ischemia and reperfusion. Long duration ischemia depletes energy of the tissue cells and decreases their ability to regenerate metabolites. The metabolism of skeletal muscle changes from oxidative phosphorylation to anaerobic glycolysis to create energy and maintain homeostasis. This transition results in lactate production and consumption of glucose and pyruvate (30). Glucose, lactate, pyruvate, and lactate/pyruvate (L/P) ratio are used as indicators of ischemia; whereas glycerol, which is mainly derived from the degradation of cell membrane phospholipids, reflects cell damage (31-33). The time limit of tolerable ischemia varies according to the type and temperature of the tissue (34). The time limit of skeletal muscle is 4 hours, shorter than those of nerve, fat, skin and bone (35).

When the oxygenated blood flow is reperfused into previously anoxic cells, toxic reactive oxygen species (ROS) are generated and cause direct cell injury by lipid peroxidation, leukocyte activation, chemotaxis and leukocyte-endothelial adherence (36, 37). In addition, ischemia promotes expression of pro-inflammatory gene products (e.g., leukocyte adhesion molecules, cytokines) and bioactive agents (e.g., endothelin, thromboxane A2), while suppresses protective gene products (e.g., constitutive nitric oxide syn-

thase, thrombomodulin) and bioactive agents (e. g., prostacyclin, nitric oxide), leading to inflammatory state that makes the ischemic tissue more vulnerable to further injury on reperfusion (38). Ischemia-reperfusion injury results from various mechanisms concerning physiological, biochemical and immunological changes (27). A schematic diagram showing the pathophysiologic changes during ischemia-reperfusion injury is provided in Figure 1 (38).

Muscle Swollen, Atrophy and Functional Recovery

In the early period of reperfusion, the involved leg becomes swollen and, in the later period, muscle atrophy develops (39). Muyskens et al. (40) analyzed histological biopsies taken from patients before TKA and at 2 hours after tourniquet deflation and found that the mean cross-sectional area of all three types (Type I, IIa, and IIx) of muscle cells increased significantly after surgery, indicating that these muscle cells were swollen. This was attributed to the depletion of energy and the dysfunction of Na/K pump, which fails to maintain transmembrane osmolarity difference. Muscle swollen is associated with weak strength. A systematic review (26) found that, when compared with patients in the non-tourniquet group, those in the tourniquet group were less likely to achieve a straight-leg raise and a better range of motion during the early postoperative period (from postoperative days 1 to 7).

Muscle loss and weakness may persist after TKA with tourniquet (41), and this hinders postoperative functional recovery (42). Dreyer et al. (43) compared the quadriceps volume from baseline to 2 to 6 weeks after TKA using magnetic resonance imaging and found a 14% reduction in 2 weeks and an 18% reduction in 6 weeks after surgery, together with significant decreases in the strength. Similar results are also reported by others (17, 44, 45). For example, Dennis et al. (45) found that the strength of quadriceps was lower in the tourniquet group than in the non-tourniquet group at 3 weeks and 3 months after TKA; and in the study of Ejaz et al. (17), early functional recovery was faster after TKA without tourniquet. However, evidence regarding the use of tourniquet in TKA and the recovery of short-term postoperative function is still limited (44) and further studies are required.

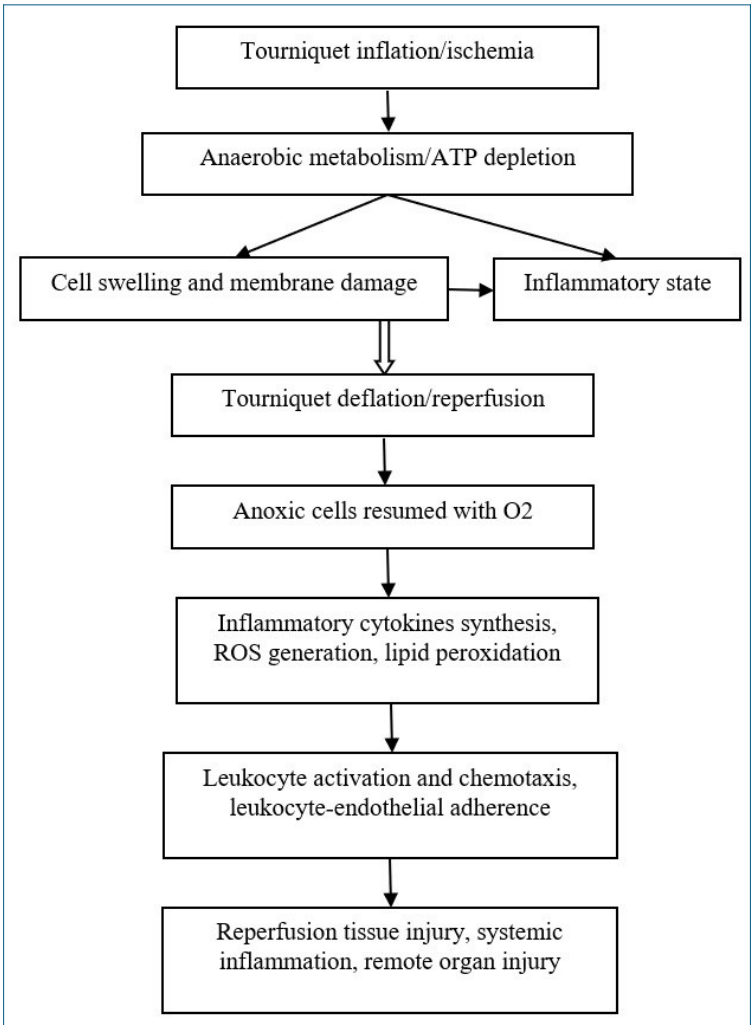

Figure 1. Pathophysiological Changes of Ischemia-Reperfusion Injury.

Systemic Inflammation and Remote Organ Injury

Ischemia-reperfusion of the lower limb produces oxidative stress and inflammatory reaction; the resulting systemic inflammation can affect distant non-ischemic organs and eventually lead to multiple organ injuries (46-48). In an animal study of Yassin et al. (49), male Wistar rats were divided into five groups, i.e., control, 3 hours of bilateral hindlimb ischemia, and 3 hours of bilateral hind limb ischemia followed by 1, 2, or 3 hours of reperfusion. They reported significant increases of plasma TNF-α and IL-6 levels in animals after ischemia and reperfusion when compared with control or ischemia alone animals. Serum ALT, AST, LDH, urea and creatinine were

also higher in reperfused animals, indicating hepatic and renal injury. Lung examination revealed capillary congestion and polymorphonuclear infiltration in animals subjected to ischemia and 3-hour reperfusion, indicating lung injury. In clinical studies, Lin et al. (50) found increases in the circulating malondialdehyde, IL-6, and IL-8, and impaired pulmonary gas exchange after tourniquet-induced lower limb ischemia-reperfusion; indicating the development of systematic inflammation and pulmonary injury after lower limb surgery with tourniquet.

Other Complications

Strong evidence supports that the use of tourniquet in TKA increases short-term postoperative pain (29). In a meta-analysis, tourniquet use during TKA increases the incidences of deep vein thrombosis (DVT) and minor complications including skin vesicles, ecchymosis, wound oozing, hematoma, nerve palsy, meralgia, ankylosis, drop foot, and delayed incisional healing (26). Other complications including acute pulmonary embolism after tourniquet release (51), peripheral nerve injury (mainly affecting peroneal or tibial nerves) after long-duration tourniquet use (7), and serious skeletal muscle injury including compartment syndrome and crush syndrome after prolonged ischemia are also reported (52).

How to Reduce Ischemia-Reperfusion Injury Induced By Tourniquet

Do Not Use the Tourniquet during TKA

Surgeons should carefully evaluate the potential benefits and risks when making the decision.

Shorten the Duration of Tourniquet Use

In a randomized controlled trial of Fan et al. (53), shortened tourniquet use decreased the degree of limb swelling and the severity of pain score, and increased the range of motion during the early period after TKA. In a meta-analysis involving 16 randomized controlled trials with 1, 170 patients undergoing TKA, Zan et al. (54) compared outcomes of tourniquet release before and after wound closure. The results showed that tourniquet release before wound closure prolonged surgical duration, and increased total as well as postoperative blood loss; however, early tourniquet release decreased the incidence of minor complications (did not require second operations) and marginally decreased the incidence of major complications (required second operations, $P=0.05$) after surgery. Similar results were also reported in the meta-analyses by others (55, 56). Therefore, the duration of tourniquet inflation should be kept as short as possible.

Measures to Attenuate Ischemia-Reperfusion Injury

Effects of Anesthetics and Anesthesia Methods

Carles et al. (57) reported that interstitial glycolysis metabolites (glucose, lactate, and pyruvate) in the skeletal muscle during ischemia and reperfusion were higher after sevoflurane anesthesia than after propofol anesthesia. Kosucu et al. (58) compared the effects of spinal, inhalational, and total intravenous anesthesia (TIVA) in patients undergoing arthroscopic knee surgery with tourniquet. They found that plasma levels of malondialdehyde and ischemia-modified albumin (metabolites of oxidative stress) were lower in the TIVA group than in the inhalational and spinal groups. In other studies, sedation with propofol, ketamine, or propofol-ketamine combination during spinal anesthesia attenuated tourniquet-induced injury (such as lipid peroxidation) in patients undergoing TKA (59-61). On the other hand, conflicting results are reported when dexmedetomidine is administered in preclinical and clinical studies (62-64). In a systematic review, Halladin et al. (65) concluded that, among various anesthetics, propofol may have a beneficial effect in reducing oxidative stress. But whether it can improve clinical outcome needs further study.

Antioxidant Intervention

Following reperfusion and activation of oxidative stress, the antioxidant enzyme system is mobilized to scavenge the reactive oxygen species (ROS). Theoretically, providing antioxidants may be helpful in reducing ischemia-reperfusion injury. Indeed, studies found that administration of N-acetyl-cysteine attenuated tourniquet-induced lipid peroxidation during arthroscopic knee surgery (66), high-dose vitamin C also provided similar effects (67); whereas mannitol was not help-

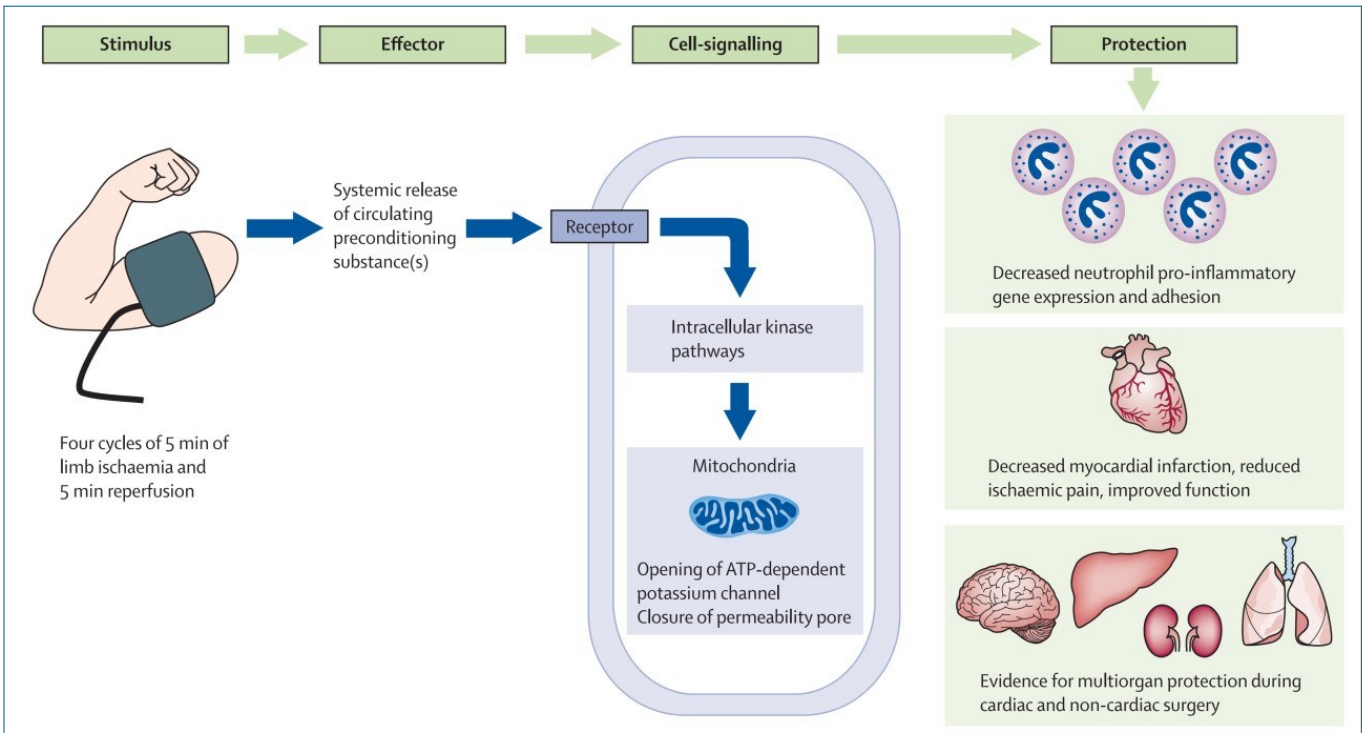

Figure 2. Remote Ischemia Preconditioning Model.
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ful in reducing oxidative parameters (8). However, studies in these aspects are still limited and whether antioxidant intervention can improve clinical outcomes needs to be demonstrated.

Ischemic Preconditioning

The effects of ischemic preconditioning in attenuating ischemia- reperfusion injury and protecting remote organs have been reported in experimental studies using various animal models (68, 69). The possible mechanisms may include increasing the release of prostacyclin and nitric oxide, inhibiting the severity of oxidative stress, and decreasing neutrophil activation, cytokine production and apoptosis (70).

The effect of local ischemic preconditioning has been examined in clinical studies. In the trial of Murphy et al. (71), local ischemic preconditioning was induced by three cycles of 5-minute tourniquet inflation and 5- minute reperfusion on the upper thigh of the operative limb and the tourniquet pressure was set at 100 mmHg above the patient's systolic blood pressure. The results showed ischemic preconditioning induced a protective genomic response, which resulted in increased expression of immediate early response genes, oxidative stress defense genes and pro-survival genes. Similar local ischemic preconditioning was performed by Lin et al. (50) and found that pulmonary gas exchange deterioration was less significant and plasma malondialdehyde, IL-6, and IL-8 were lower in the ischemic preconditioning group than in the non-ischemic preconditioning group, indicating attenuated pulmonary dysfunction, lipid peroxidation and systemic inflammatory response.

The mechanisms of remote ischemic preconditioning are different from local ischemic preconditioning but may be also effective (see Figure 2) (72, 73). The study of Aktaş et al. (74) enrolled patients undergoing bilateral TKA under tourniquet and initiated surgery from the right side. The left tourniquet was inflated 20 minutes after the right tourniquet was deflated. The results showed a less severe postoperative oxidative stress and better knee function (assessed with the

WOMAC score) in the left side, possibly produced by the right side ischemic preconditioning.

In the systematic review of Halladin et al. (65), it is also concluded that ischemic preconditioning may have some benefit in reducing oxidative stress after surgery under tourniquet; but, again, the impact of such effects on postoperative clinical outcomes need to be further investigated.

Summary

Use of tourniquet during TKA reduces intraoperative blood loss and requirement of blood transfusion and shortens duration of surgery. However, tourniquet induced ischemia-reperfusion injury produces harmful effects to the involved limb (muscle swollen and atrophy and persistent weakness) and remote organs (thrombosis, lung injury, wound complications, etc.). The benefits and risks of the tourniquet use should be carefully evaluated before making the decision. For patients who have to use tourniquet during surgery, shorten the ischemic duration can attenuate the severity of ischemia- reperfusion injury. Propofol sedation and ischemic preconditioning may be helpful in reducing oxidative stress but effects on clinical outcomes need to be investigated further.

The author declares no conflicts of interest.

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