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Original Article

Preliminary feasibility study of a new method of hypothermia in an experimental canine model

Yeni bir renal hipotermi sisteminin deneysel köpek modelinde ön fizibilite çalışması

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ABSTRACT

Objective: To build up a new microcontroller thermoelectric system to achieve renal hypothermia.

Material and methods: Renal hypothermia system was tested under in vivo conditions in the kidneys of ten Mongrel dogs. Ambient temperature was evaluated using two different microcontrollers. In order to ensure hypothermia in the renal parenchyma, selection can be made among 4 modules and sensors which detect the temperature of the area. The temperature range of the system was adjusted between -50°C and +50°C.

Results: When single and double poles of the kidney were cooled, initial mean intraperitoneal temperature values were found 37.7°C for rectum and 36.5°C for renal cortex and medulla. After the temperature of the cooling module was set to 12°C, the module was placed on the poles of the kidney. After fifteen minutes, temperature was 15.4°C in the lower pole of the kidney, 28.1°C in the cortex of the other side and 29.2°C in the intramedullary region. The temperature was found to be 15°C in the vicinity and 26.1°C in the cortex across the module. After the system was stabilized, a very slight change was observed in the temperature.

Conclusion: Hypothermia system developed ensured desired cooling of the targeted part of the kidney; however, it did not cause a change in the temperature of other parts of the kidney or general body temperature. Thus, it was possible to create a long-term study area for renal parenchymal surgery.

Keywords: Hypothermia; partial nephrectomy; renal surgery; thermo-electric system.

ÖZ

Amaç: Renal hipotermi sağlamak amacıyla yeni bir mikro-kontrolörlü termoelektrik sistem geliştirmek.

Gereç ve yöntemler: Renal hipotermi sistemi on adet Mongrel türü köpeğin böbreğinde in vivo ortamda test edilmiştir. Sıcaklık değeri iki farklı mikro-kontrolör ile değerlendirilmiştir. Renal parankimde hipotermi sağlayabilmek için alan sıcaklığını belirleyen birden dörde kadar modül ve sensör seçilebilmektedir. Sistemin sıcaklık aralığı -50°C ve +50°C arasında ayarlanmıştır.

Bulgular: Böbreğin hem tek hem de çift polü soğutulmadan önce başlangıç ortalama intraperitoneal sıcaklık değeri rektumda 37,7°C, renal korteks ve medullada ise 36,5°C olarak tespit edilmiştir. Soğutucu modülün sıcaklığı 12°C'ye ayarlandıktan sonra böbrek polüne yerleştirilmiştir. Onbeş dakika sonra sıcaklıklar böbrek alt polünde 15,4°C, karşı taraf kortekste 28,1°C ve intramedüller alanda ise 29,2°C olarak kaydedilmiştir. Modül çevresinde sıcaklığın 15°C, modül karşısındaki kortekste ise 26,1°C olduğu gözlenmiştir. Sistem stabilize edildikten sonra sıcaklık değerlerinde sadece çok hafif değişmeler olduğu gözlenmiştir.

Sonuç: Geliştirilen hipotermi sistemi böbreğin hedeflenen bölgesinde istenilen soğutmayı sağlamıştır. Bununla birlikte, böbreğin diğer bölümlerinde veya genel vücut sıcaklığında herhangi bir değişikliğe sebep olmamıştır. Bu nedenle de renal parankim cerrahisi için uzun süreli bir çalışma alanı yaratmak mümkün olmuştur.

Anahtar Kelimeler: Hipotermi ; parsiyel nefrektomi; renal cerrahi; termo-elektrik sistem.

Introduction

Partial nephrectomy (PN) has become the gold standard procedure for the treatment of small renal tumors (especially <4 cm), and will be performed more commonly as the incidence of incidentally diagnosed small renal tumors increases.[1] Open partial nephrectomy (OPN) is advised much more as recent literature has showed that nephron-sparing surgery (NSS) has the advantages of improved renal function and prolonged life expectancy.[1]

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Nowadays minimally invasive NSSs, such as laparoscopic partial nephrectomy (LPN) and a much newer technique of robotic partial nephrectomy (RPN), are being performed increasingly parallel to the developments in the technology. Cooling the kidney is more difficult and complex in LPN, and mean ischemia time is generally longer than OPN. This problem has been overcome to some degree in RPN with the technical properties of the robotic surgery system.[2]

Providing a bloodless operative field and preventing renal dysfunction during the postoperative period are the most important issues in long-lasting renal parenchymal surgery. The easiest method used for this purpose is clamping the renal artery, which has a disadvantage of limited time of only 30 minutes in order to avoid loss of renal function.[3] This time can be extended in a hypothermic setting.

Among other methods used for hypothermia up to now, the one that has been most frequently and easily used is the *in situ* cooling of the renal surface by external ice-slush.[4] In this surface hypothermia method, it is difficult to maintain the temperature at the same level in the renal cortex and this method may lead to renal injury. Another method is to provide hypothermia by a cooling instrument that is completely wrapped around the kidney.[5] Besides these methods, there are invasive techniques such as renal artery perfusion and retrograde endoscopic renal hypothermia.[6-8]

The aim of this study was to noninvasively create an ideal state of renal hypothermia (RH) which will ensure ideal hypothermia setting in distant parts of the renal cortex and medulla, and maintain the targeted level of temperature at a certain part of the kidney for a particular period of time.

Material and methods

The protocol of this experimental study was approved by the Selçuk University Animal Experiments Ethics Committee (approval number: 2013.HDEK.2010008), and it was performed in accordance with principles of laboratory animal care in the Selçuk University School of Veterinary Medicine.

In this study, a RH system was controlled by using two 8-bit separate microcontrollers, PIC16F84 and PIC16F877 in compliance with MPASM package program. The temperature value obtained from the PIC16F84 outlet was fed to the second microcontroller PIC16F877. A 10-bit counter that can be adjusted as 4 ups-downs separately between 0 and 700 was placed in PIC16F877 in order to determine the temperature value at different parts of the kidney. Thus, not only the temperature of the area could be adjusted by its own counter, but also the thermoelectric module and the sensors that perceive the temperature of these modules could be selected.

Microcontroller calculated the difference between the adjusted temperature and the actual temperature. This difference was multiplied by the system's proportional gain, to obtain the proportional tension which was used as the control tension that changes duty cycle of the Switch Mode Power Supply (SMPS). When the control tension of SMPS was proportionally altered, the outlet tension automatically changed proportionally. This tension fed the thermoelectric module in the selected area. The system was equipped with a continuous cycle, required for cooling in thermoelectric systems.

A serpentine formed from a 4-mm copper tube was mounted at the opposite side of the module's surface cooling the kidney. Water at room temperature was pumped through a plastic pipe to the serpentine, which traveled along the serpentine and returned to the depot. Thus, the temperature of the module was maintained at a stable level. In case of the presence of insufficient water in the system or sensor errors, alarm system would be automatically activated and give a sonorous warning. Moreover, the type of the error can be monitored from the Liquid Crystal Display (LCD) monitor. When the temperature value in the system reaches or exceeds the warning limit, the alarm system is activated. The temperature range can be adjusted between -50°C and +50°C, and the system can readily provide the ideal temperature value of hypothermia (15°C) within 15 min. When the temperature of a module reaches the desired cooling value, the system can maintain the same temperature for as long as necessary.

The main body of the system covers an area of 50x25x25 cm. Each module is square in shape and 3x3x0.3 cm in size. It can be used in the form of a box that can house renal poles depending on the modular position. The development of this system and the initial successful experience obtained with it, was published previously.[9]

The system was tested for 60 min at room temperature in order to provide hypothermia in the kidneys of ten Mongrel dogs, divided into two groups as Groups 1, and 2, in the Research and Development Laboratory of Selçuk University, School of Veterinary Medicine. The dogs were anesthetized by intramuscular administration of xylazine hydrochloride 2 mg/kg + ketamine hydrochloride 20 mg/kg, and then transperitoneal incisions were made. The median dimensions of the kidneys of the dogs were measured as 6.8x4.3x2.9 cm. At the beginning of the operation, renal pedicle was freed and clamped. Sensors were placed in the lower and upper poles of the kidney, opposite side of the thermoelectric module and intra-medullary areas. The module, which was sterilized with ethylene oxide gas, was placed at the lower poles of the kidneys in Group 1, and at the lower and upper poles of the kidneys in Group 2 (Figure 1). Schematic view and application of the developed RH system are presented in Figure 2.

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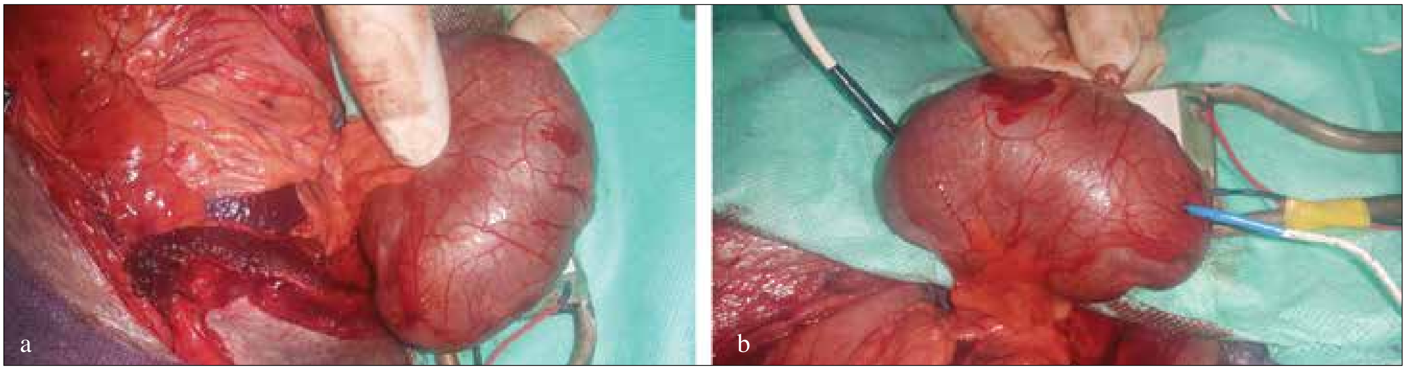

Figure 1. a, b. Intraoperative pictures showing the application of the developed system and measurement of the temperature. (a) The kidney is dissected, mobilized, and placed on the cooling module. (b) The temperatures of the upper and lower poles are being measured

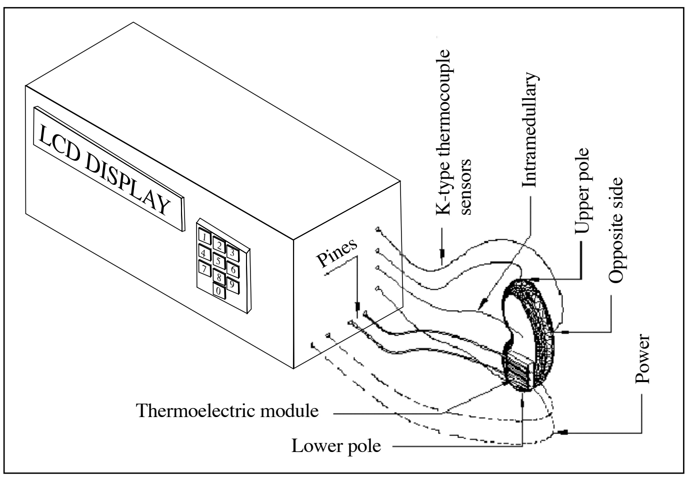

Figure 2. Schematic external view of the developed system

Temperatures measured by thermocouple near the module, at the opposite side of the module, upper pole and intra-medullary areas were recorded. The measurements were repeated for a total of 13 times, once at the beginning and then every 5 min thereafter. Mean values were calculated and possible measurement errors were minimized. In addition, body temperature was rectally measured every 5 min for 60 min.

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences for Windows® Version 15.0 (SPSS Inc.; Chicago, IL, USA). Statistical analysis was based on paired t test, Wilcoxon signed ranks test and Mann-Whitney U test where applicable. A p value of <0.05 was considered as statistically significant.

Results

Table 1 presents the mean time-dependent average temperatures measured from different areas of the kidney during the operation using the newly developed RH system for the Group 1, and Table 2 shows the corresponding values for Group 2.

As demonstrated in Tables 1 and 2, it was found that although renal parenchymal surgery could be performed by cooling only one pole, cooling both poles produced better results. Double-pole cooling system should be preferred in interventions that will last more than 60 min.

It was found that the kidney surface where only one module was placed, returned to its normal initial temperature within 5 min. and other areas within 2 min. after the renal clamp was removed. It was also established in this experiment that the double module-cooled areas returned to their normal initial temperatures with only a slight time difference. When the experiment was completed, the dogs were awakened and kept alive, and no complication was observed during the postoperative period.

As shown in Figure 3, in both single and double-pole cooling systems, temperatures of the cooled areas significantly decreased within 15 min. and remained fixed approximately for 60 min. There was a slight decrease in the temperatures of other areas that also remained fixed. General body temperature did not change throughout the procedure.

Discussion

Partial nephrectomy has become the gold standard treatment in the management of small renal tumors.[1] NSSs, whether open or minimally invasive, are being performed more commonly as much more small renal tumors are incidentally diagnosed. The major problems in renal parenchymal surgery are hemorrhage and loss of renal function. Researchers studying in the field of renal surgery aim at finding a bloodless and long-lasting method of hypothermia that does not result in renal dysfunction.

Table 1. Average temperature values of the cooled lower poles of the kidneys in Group 1

Time (min)	Rectal Temp. (°C)	Lower Pole Temp. (°C)	Opposite Side Cortical Temp. (°C)	Upper Pole Temp. (°C)	Intramedullary Temp. (°C)
0	37.7	36.4	36.3	36.4	36.4
5	37.6	34.7	35.6	35.8	35.9
10	37.6	29.2	31.3	32.2	31.1
15	37.5	15.7	30.1	31.3	30.2
20	37.5	15.2	28.3	30.4	29.5
25	37.5	15.0	28.1	29.2	29.1
30	37.5	15.3	28.0	29.3	29.3
35	37.4	15.2	28.3	29.3	29.4
40	37.4	15.0	28.1	29.0	29.2
45	37.4	14.9	28.0	29.1	29.4
50	37.3	15.1	28.2	29.3	29.2
55	37.3	15.2	28.2	29.1	29.3
60	37.3	15.0	28.1	29.2	29.1

Table 2. Average temperature values of the cooled lower and upper poles of the kidneys in Group 2

Time (min)	Rectal Temp. (°C)	Lower Pole Temp. (°C)	Opposite Side Cortical Temp. (°C)	Upper Pole Temp. (°C)	Intramedullary Temp. (°C)
0	37.6	36.6	36.6	36.6	36.6
5	37.6	29.4	33.1	29.5	35.5
10	37.6	22.2	29.3	22.2	31.1
15	37.5	15.1	26.1	15.3	28.2
20	37.4	15.2	24.3	15.4	26.5
25	37.4	15.0	24.1	15.2	25.1
30	37.4	15.3	24.0	15.3	25.3
35	37.3	15.2	23.3	15.3	25.4
40	37.3	15.2	23.1	15.0	25.2
45	37.2	15.1	22.0	15.1	25.4
50	37.2	15.1	22.3	15.3	25.2
55	37.2	15.1	20.2	15.1	24.3
60	37.2	14.9	20.1	15.2	24.1

Renal cortex and medulla are vulnerable to the damages related to ischemia.[10] Tissue ischemia causes the release of various inflammatory and vasoactive products that cause further damage, and continued ischemia leads to cell death.[10] Because renal metabolic activity is almost completely suspended at temperatures of 5°C to 20°C, the goal of RH should be to provide a renal temperature within this range in order to minimize ischemia related organ damage. In the past, Ward[11] has established that optimal RH is 15°C, which is not easy to achieve.

Although the easiest method to provide a bloodless situation is clamping the renal artery, this method has a disadvantage of limiting the operation time to 30 min in order to avoid renal dysfunction.[3] Although there is a common generalization that warm ischemia time (WIT) for over 30 min. leads to renal dysfunction, a recently well-designed small prospective study has shown that 25 min is a cut-off value in WIT for irreversible renal damage.[12] In addition to this, a recent publication suggests that every minute of warm ischemia can affect the risk of developing stage IV chronic kidney disease.[13]

It has been reported that arterial occlusion at 20°C has provided an operation time up to 2 hrs in practice and this time interval has been extended up to 4 h in some cases by opening and clos-

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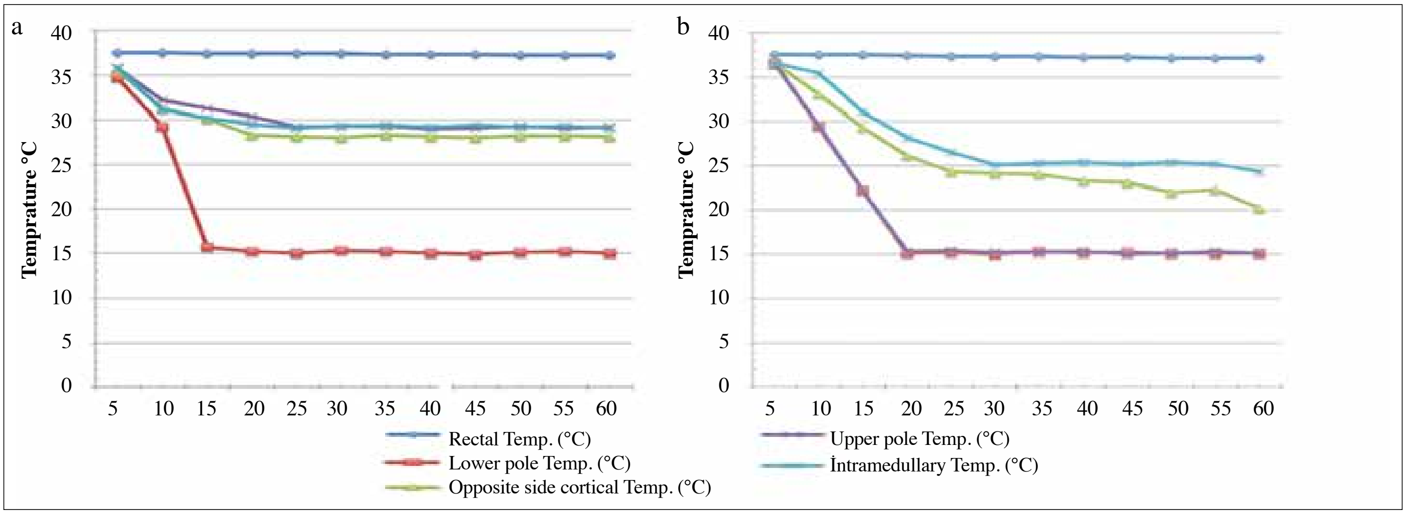

Figure 3. a, b. (a) Time/average temperature graphs of the values obtained when only lower pole is cooled. (b) Time/average temperature graphs of the values obtained when lower and upper poles are cooled at the same time

ing the artery.[11] However, in contrast to this, there is evidence in the literature that intermittent clamping of the renal artery with short periods of recirculation may also be more damaging than continuous arterial occlusion.[14]

In the surface hypothermia obtained with ice-slush, a volume of about 300-750 mL is required and 15 min should be ensured in order to cool the cortex. This leaves 5-20 min time for manipulation. It is difficult to keep the cortical temperature at the same level since the ice-slush warms up very rapidly, thus a stable hypothermia cannot be provided in all parts of the kidney. Besides, there is a loss of temperature in the tissues near the kidney contacting with the ice-slush.[4] Against its disadvantages, this method has been used commonly in open surgery as it is easy and cheap to apply.

In retrograde endoscopic RH, cold saline serum was cooled down to -1.7°C and circulated by the retrograde urethral route. Meanwhile, the temperature measured by thermocouple was 24°C in the cortex and 21°C in the medulla. This method lengthened the operation time for 35 min, but it must not be forgotten that it is an invasive method. Landman et al.[8] reported the clinical technique and preliminary results of efficacy of RH achieved by high-flow retrograde instillation of ice-cold saline.

An invasive method of renal parenchymal cooling has been introduced by Marberger et al.[6,7] They described this effective cooling method, in which the renal artery had been occluded intraluminaly by a balloon-tipped catheter and the kidney had been cooled by an intermittent hypothermic perfusion, in 26 of 31 extensive nephrolithotomies.[6] In their second paper, they again showed that percutaneous transarterial hypothermic renal perfusion was superior to topical ice-slush hypothermia in terms of recovery of postoperative renal function as demonstrated in 95 extensive nephrolithotomies.[7] The applicability of this method in LPN, with a modification of arterial occlusion by applying a tourniquet on renal artery was shown by Janetschek et al.[15] With their initial experience in a series of 15 patients, they concluded that this method was safe and feasible in LPN. Later on, Shen et al.[16] reported that renal arterial catheterization for temporary balloon occlusion and hypothermic perfusion of renal artery was safe, effective and feasible in LPN with postoperative kidney function being comparable to the preoperative values. Marley et al.[17] have demonstrated that intravascular perfusion with ice-cold lactated Ringer's solution during LPN can achieve RH below 15°C with minimal changes in renal functions during the early postoperative period.

One of the studies aiming to provide an effective hypothermia on the renal cortical surface was conducted by Cockett et al.[5] by using an external cooling device. They developed a stainless steel surface cooler with a kidney-like shape, which cooled the completely mobilized kidney to 7-10°C during PN while protecting the renal pedicle and ureteropelvic junction. This external device, manufactured in three different sizes, was found to be effective for ensuring cold ischemia.[5]

Several cooling devices have been developed later on, and some of them have been patented. Herrell et al.[18] have developed a cooling sheath device with a bag containing ice slurry, which can be used for either open or laparoscopic surgery, and have shown that this device could protect the kidney hypothermically during 60 min of temporary arterial occlusion in a laparoscopic swine model. This device was difficult-to-use because of the tubing placement and bag size, and did not get a patent despite its application. Thomas et al.[19] granted a patent in 2010 for their cooling device consisting of a bag with a fluid reservoir in which the kidney can be placed. Despite the preliminary promising results, none of these devices have been studied further, marketed, or seen wide adoption.

Summers et al.[20] have designed, prototyped and evaluated the effectiveness of a minimally invasive renal cooling device consisting of a fluid-containing bag with foldable cooling surfaces. This device was deployed through a 15-mm trocar and wrapped around the kidney. The bag was filled with ice slurry and remained on the kidney for up to 20 min. The researchers showed that the device successfully cooled porcine kidneys from 37°C down to 20°C in 6 to 20 min.[20]

In our study, it was planned to develop a noninvasive RH system that could keep a targeted part of the kidney at a certain temperature for as long as necessary. Renal cortex can be cooled down to the intended temperature values, totally or locally, and the temperature of the cooling module reaches to the desired level for application in as shortly as 3 min. Cooling modules can be used in two opposite sides of the kidney at the same time. After the temperature of the module reaches the targeted cooling value, the same temperature can be stably maintained. It is contemplated that the system not only prolongs the operation time, but also confers all advantages of hypothermia. Since the parts of the module not used for cooling are isolated, it does not have any influence on the body temperature or the tissues around the kidney.

Our study has certainly some limitations. Firstly, the dog model may not be applicable to humans, as the dog kidneys are smaller than the adult human kidneys. The increased mass of the human kidney may make it more difficult to cool in that it either requires a longer period of time to cool or it is not possible to cool the kidney to 15°C using this system. Secondly, this system is useful for only open surgery at the moment. A new different version can be developed for minimally invasive surgery in the future with further researches focusing on decreasing the size of the modules so as to make it possible to advance the modules through trocars.

In conclusion, the developed RH system brings any part of the kidney to the targeted temperature within 15 min and reliably maintains that temperature for the predetermined period of time. No significant temperature changes take place in other parts of the kidney and general body temperature is not affected, either. It has been observed that this system can simply ensure extra RH in the targeted way. Further studies should be conducted on various animal kidneys before trying this system in humans.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selçuk University Animal Experiments Ethics Committee (approval number: 2013. HDEK.2010008).

Informed Consent: No informed consent was required as no patients were used in this study.

Peer-review: Externally peer-reviewed.

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