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Comparison of the WarmCloud and Bair Hugger Warming Devices for the Prevention of Intraoperative Hypothermia in Patients Undergoing Orthotopic Liver Transplantation: A Randomized Clinical Trial

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Background. The avoidance of hypothermia is vital during prolonged and open surgery to improve patient outcomes. Hypothermia is particularly common during orthotopic liver transplantation (OLT) and associated with undesirable physiological effects that can adversely impact on perioperative morbidity. The KanMed WarmCloud (Bromma, Sweden) is a revolutionary, closed-loop, warm-air heating mattress developed to maintain normothermia and prevent pressure sores during major surgery. The clinical effectiveness of the WarmCloud device during OLT is unknown. Therefore, we conducted a randomized controlled trial to determine whether the WarmCloud device reduces hypothermia and prevents pressure injuries compared with the Bair Hugger underbody warming device. **Methods.** Patients were randomly allocated to receive either the WarmCloud or Bair Hugger warming device. Both groups also received other routine standardized multimodal thermoregulatory strategies. Temperatures were recorded by nasopharyngeal temperature probe at set time points during surgery. The primary endpoint was nasopharyngeal temperature recorded 5 minutes before reperfusion. Secondary endpoints included changes in temperature over the predefined intraoperative time points, number of patients whose nadir temperature was below 35.5°C and the development of pressure injuries during surgery. **Results.** Twenty-six patients were recruited with 13 patients randomized to each group. One patient from the WarmCloud group was excluded because of a protocol violation. Baseline characteristics were similar. The mean (standard deviation) temperature before reperfusion was 36.0°C (0.7) in the WarmCloud group versus 36.3°C (0.6) in the Bairhugger group ($P = 0.25$). There were no statistical differences between the groups for any of the secondary endpoints. **Conclusions.** When combined with standardized multimodal thermoregulatory strategies, the WarmCloud device does not reduce hypothermia compared with the Bair Hugger device in patients undergoing OLT.

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During orthotopic liver transplantation (OLT) surgery, maintaining normothermia is challenging due to a large open wound cavity, prolonged surgical time, large volume of fluids infused, reduced metabolic activity due to the exclusion of the liver during the anhepatic stage, and the significant thermal stress of the introduction of a donor liver which has been stored in an ice bath.

Quality randomized controlled trials have linked hypothermia to poor clinical outcomes such as delayed wound

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Prospectively registered with the Australian Clinical Trial Registry (ACTR No. 12614000953639) on 5th September 2014.

Hoyland Medical Pty Ltd (Murrarie, Australia), the Australian Distributors of the WarmCloud provided the Base Unit of the WarmCloud device on loan for the duration of the trial and provided 10 free disposable mattresses, of which 8 were used in the trial. The remaining mattresses were purchased. While Hoyland Medical were aware that we were conducting this trial they were not involved at any stage and in particular had no input into the trial design, data collection, analysis or writing of the manuscript.

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healing and infections,[1,2] impaired coagulation,[3] reversible platelet dysfunction,[4] increased blood loss and transfusion requirements,[5] and a higher risk of cardiac morbidity.[6] However, the largest intervention review investigating active body surface warming systems for preventing hypothermia in adults[7] concluded that it was unknown which type of warming device is most effective.

At our institution, we routinely use several devices during liver transplantation to prevent hypothermia. Fluids are heated using a rapid infusion device (Belmont Rapid Infuser, Belmont, Billerica, MA) and/or a Hotline fluid warmer (Smiths Medical, Minneapolis, MN). An underbody Bair Hugger forced air warming blanket (Bair Hugger 3M, Model 637; Maplewood, MN) is used which distributes warm air at 43°C around the body. A heat and moisture exchange filter is inserted into the ventilation tubing, and the patients' arms are wrapped in towels. Despite all of these measures, normothermia during OLT remains elusive.[8]

The WarmCloud device (KanMed, Bromma, Sweden) is an underbody warming device that consists of a heating unit with a fan that drives warm air through a soft mattress located underneath the patient. However, rather than having holes in the mattress, as the Bair Hugger system has, the WarmCloud mattress is pressurized, and creates a soft, temperature-controlled cushion. The proposed benefits include a larger direct contact area with the patient, resulting in transfer of heat directly to the patient using simple conduction physiology principles. We proposed that the WarmCloud system would reduce the degree of hypothermia during liver transplantation compared with Bair Hugger device when standard multimodal strategies were used to maintain normothermia in patients undergoing OLT.

MATERIALS AND METHODS

After approval from the Austin Health Research Ethics Committee (HREC no: LNR/14/Austin/306), we performed a prospective, randomized controlled trial of adult patients undergoing primary OLT. We prospectively registered the trial with the Australian Clinical Trial Registry (ACTR No: 12614000953639, registered May 9, 2014). Inclusion criterion included adult patients (age, > 18 years) undergoing primary OLT. We excluded patients undergoing multivisceral transplantation, patients with fulminant liver failure and those with a preoperative or intraoperative requirement for continuous venovenous bypass or hemofiltration. All patients underwent comprehensive preoperative anesthesia and surgical evaluation at a dedicated OLT preadmission clinic.

Standardization of Perioperative Temperature Homeostasis

Preoperative temperature homeostasis was standardized for all participants as previously reported by our research group.[8] Ambient room temperature was set at 21°C to 22°C using a thermostatic control. Participants were randomized to either the WarmCloud device, or the Bair Hugger device. In addition, standard multimodal strategies to maintain normothermia (as described above) were used in both groups. Each device was applied before induction of anesthesia and for a period of at least 60 minutes before skin incision.

The maximum temperature setting of the WarmCloud is 42°C and this was the default setting used. The Bair Hugger was used at its maximum temperature of 4°C. If the patient's temperature rose above 37.0°C, the Bair Hugger was turned down to 32°C, and if the patient's temperature rose above 37.4°C, it was turned to ambient. Similarly, for patients in the WarmCloud group, the temperature was reduced to 32°C when core temperature reached 37.0°C, and if the temperature exceeded 37.4°C, the device was reduced to 22°C. It is noteworthy that the WarmCloud, unlike the Bair Hugger, should never be switched off to maintain the pressurized air effects that the device confers to the patients. Further, turning the WarmCloud off may affect the position of fixed retractors relative to the tissues resulting in trauma. If a participant in either group reached a temperature below 35.5°C an upper body BairHugger was added. Anesthesia and surgery were standardized for all participants as previously reported.[8]

Core temperature was measured by a nasopharyngeal temperature probe (CareFusion Incorporation, Australia) inserted in the upper third of the nasopharynx.[9] Nasopharyngeal temperature has been reported to be a simple, reliable, and precise measurement of core body temperature.[10-12] Temperature measurements were documented every 30 minutes throughout the procedure as well as at the following timepoints during transplantation: start of surgery, phase 1 + 30 minutes, phase 1 + 60 minutes, phase 2 start, phase 2 + 30 minutes, phase 3 – 5 minutes, phase 3 + 5 minutes, phase 3 + 60 minutes, and closure. The 3 phases of liver transplantation can be summarized as follows. Phase 1 commences at skin incision and concludes when the portal vein is clamped. Phase 2, the anhepatic phase, continues from this point until reperfusion of the donor organ via the portal vein. Phase 3 then continues until closure and includes hepatic artery and biliary anastamoses.

The primary endpoint was nasopharyngeal temperature 5 minutes before reperfusion. This timepoint was chosen because it provides maximum duration of use of the devices without the confounding effects of the thermal challenge introduced by reperfusing an ice-cold liver. Secondary endpoints included the average temperature changes throughout surgery, temperature at skin closure, number of patients whose nadir temperature was below 35.5°C, the number of patients who developed hyperthermia during surgery (temperature, > 37°C), and presence of any pressure injuries during surgery.

Pressure injury was graded using the Pressure Ulcer Classification System international grading system as advocated by the European Pressure Ulcer Advisory Panel and American National Pressure Ulcer Advisory Panel.[13] This grades pressure ulcers by depth and includes 4 categories: category 1, nonblanchable erythema; category 2, partial thickness skin loss or blister; category 3, full thickness skin loss with fat visible; and category 4, full thickness skin loss with muscle/bone visible.

Two independent critical care nurse practitioners, expert in the assessment of pressure injuries, assessed each patient for pressure injury on completion of surgery. For pragmatic reasons, 1 nurse practitioner assessed the patients for pressure injury immediately after surgery in the operating room. The second nurse practitioner assessed pressure injury immediately on arrival to the intensive care unit. Both assessors were blinded to the intervention. The liver transplantation register which keeps accurate records of complications in all liver transplant recipients was also cross-referenced for late-presenting ulcers.

Other data collected included age, sex, weight, body mass index (BMI), indication for transplant, Model for End-stage Liver Disease (MELD) score, duration of surgery, total volume of infused fluids, volume of red cells infused (cell salvage and packed), duration of intensive care unit stay (in hours), and duration of hospital stay (in days).

Statistics

Samples size calculations were performed using inferences for means comparing 2 independent samples. A previous audit of 60 patients at our institution, conducted over an 18-month period, in patients undergoing OLT who had a Bairhugger device used as part of standard anesthesia care for intraoperative thermoregulation, estimated that the mean (standard deviation [SD]) temperature 5 minutes before reperfusion was 35.9°C. (0.41). To demonstrate a 0.5°C difference between the groups, assuming an alpha error probability of 0.05, and a beta value of 0.8, 12 patients were required in each group. To allow for any protocol violations, we received ethics approval to recruit a total of 26 participants.

A computer-generated randomization program was used to ensure that all participants received individual randomization codes. Random permutations of treatments for each participant were created using the randomization program first generator application entering "WarmCloud Group" and "Bair Hugger Group" as the treatment labels. Participant randomization was sealed in an opaque envelope, and the envelopes were opened by study investigators before surgery. Intraoperative blinding was not feasible.

Continuous data were tested for normality using the D'Agnostino-Pearson omnibus test. For the primary end point between groups, comparisons for continuous data were performed with the Student *t* test (2-tailed). Values were reported as mean and SD or median and interquartile range. Changes in temperatures throughout surgery were measured with repeated-measures analysis of variance (ANOVA). A *P* value of 0.05 was regarded as significant for every outcome. Statistical analyses were performed using GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA). The study is reported according to the updated CONSORT guidelines for reporting parallel group randomized trials.[14]

RESULTS

The study was conducted between October 2014 and July 2015. During this period, 44 liver transplants took place at our institution. Six patients were excluded (pediatric, n = 2; fulminant liver failure, n = 2; preoperative continuous venovenous hemofiltration, n = 2). A WarmCloud disposable mattress was not available for a period excluding 5 patients, and there were no investigators present to conduct the study for 7 patients (Figure 1). In total, 26 participants were recruited with 13 participants randomized to the Warmcloud group and 13 to the Bair Hugger group. One participant, allocated to the WarmCloud group, had a Mega Soft reusable gel diathermy-conducting pad (115 × 50 cm) placed between him and the WarmCloud for the duration of surgery. This may have reduced effective conduction, and therefore, this patient was excluded from the analysis. There were 3 other minor deviations from the study protocol. The Bair Hugger was inadvertently turned off, instead of turned to ambient temperature in 3 participants who reached temperatures above 37.0°C. These participants have been included in the statistical analysis.

Groups were similar for age, BMI, and MELD scores (see Table 1). Indications for transplantation are similar between groups. The mean (SD) room temperatures was 22.2°C (1.5) in the Bair Hugger group and 22.3°C (1.8) in the WarmCloud

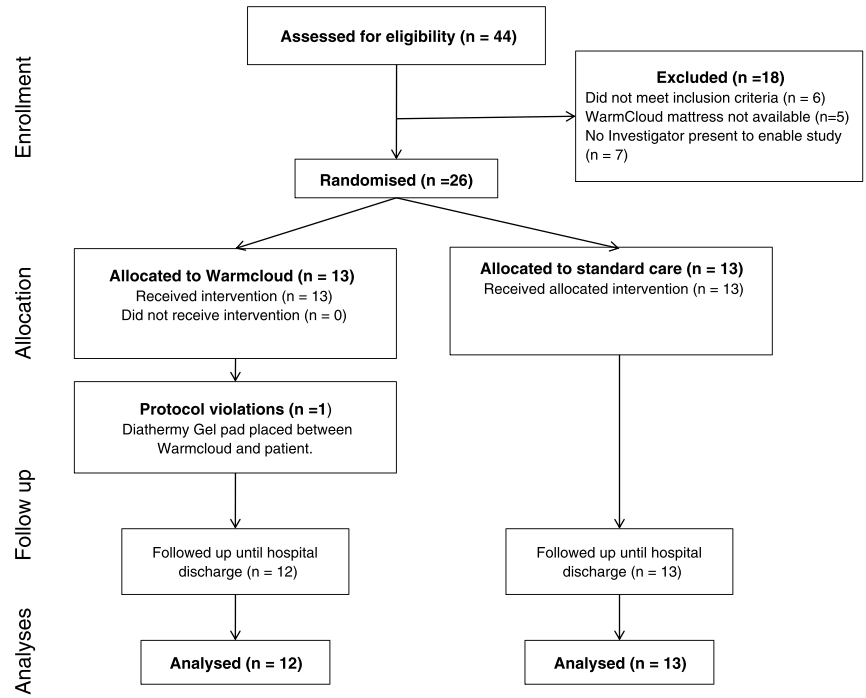

FIGURE 1. CONSORT diagram.

TABLE 1.

Participant demographics

	WarmCloud group (n = 12)	Bair hugger group (n = 13)	*P*
Age, y	54.3 (8.6)	58.9 (6.5)	0.15
Male gender	11 (92%)	9 (69%)	0.32
BMI, kg/m^2	23.9 (3.9)	27.4 (6.5)	0.20
MELD score	19.6 (8.6)	17.4 (6)	0.44
Indications for transplant			
Alcoholic cirrhosis	2	1	
Hepatitis C cirrhosis	2	1	
Hepatitis B cirrhosis	0	1	
Primary sclerosing cholangitis	2	2	
Hepatocellular carcinoma	4	5	
Cryptogenic cirrhosis	2	1	
Other	0	2	
Total duration of surgery, min	380 (72)	489 (71)	0.001
Duration of surgery until reperfusion, min	193 (71)	254 (79)	0.06
Total fluids infused, L	6.8 (4.8)	11.3 (4.8)	0.02
Red blood cells infused, L	1.7 (1.6)	3.2 (2.1)	0.08

Data presented as median (SD) or number (percentage).

group (*P* = 0.88). This was concurrent with the thermostatic control of theater temperatures stipulated in our methods. Baseline patient temperature on arrival in the operating room, and immediately before the commencement of the application of the warming devices was 36.2°C (0.6) in the WarmCloud group and 36.0°C (0.6) in the Bair Hugger group (*P* = 0.55).

For the primary endpoint, the mean (SD) nasopharyngeal temperature before reperfusion, was 36.0°C (0.7) in the WarmCloud group versus 36.3°C (0.6) in the Bair Hugger group; *P* = 0.25 (Figure 2). Mean nasopharyngeal temperatures at the end of surgery were similar: WarmCloud 36.7°C (SD, 0.7) versus 36.8°C (0.7) in the Bair Hugger group (*P* = 0.73). A graphic representation of the changes in patients' temperatures throughout each phase of surgery is presented in Figure 3. There were no statistical differences in temperatures between the groups throughout the duration of surgery (*P* = 0.25, repeated-measures ANOVA). Ten patients (83%) in the WarmCloud group and 5 (38%) patients in the Bair Hugger group reached a nadir at or below 35.5°C (*P* = 0.11) and therefore had an upper body BairHugger added as a recuse therapy as per protocol. Six patients (50%) in the WarmCloud Group and 8 (62%) patients in the Bair Hugger group reached a peak temperature of 37.0°C or greater (*P* = 0.70). There were no pressure injuries documented in either group.

The mean (SD) total duration of surgery was 380 (72) minutes in the WarmCloud Group and 489 (71) minutes in the Bair Hugger group (*P* = 0.01). There was no statistically significant difference in duration of surgery before reperfusion (WarmCloud, 193 (71) minutes vs Bair Hugger 254 (79) minutes; *P* = 0.06). The mean (SD) volume of fluid administered in the Warmcloud group was 6.6 L (4.4) versus 11.3 L (4.8) in the Bair Hugger group (*P* = 0.02). The amount of blood infused was 1.7 (1.6) L in the WarmCloud group and 3.2 (2.1) L in the Bair Hugger group (*P* = 0.08).

DISCUSSION

Our study showed that the Kanmed WarmCloud did not show a benefit in maintaining normothermia during OLT compared with the Bair Hugger device. There was a trend toward the WarmCloud being less effective than the Bair Hugger, with an average temperature difference of 0.4°C between groups before reperfusion. This was our primary endpoint. There was also no significant difference between the groups at the end of surgery or at any other timepoint. There was no significant difference in those who reached above 37.0°C or below 35.5°C.

There is only one PubMed-indexed randomized controlled trial comparing the WarmCloud to other warming devices. This trial demonstrated the WarmCloud to be less effective than another device, called the AllonTM2001 Thermowrap and no different to the Bair Hugger,[15] in a trial done on patients with severe burns. The Allon Thermowrap can wrap around any exposed body part maximizing contact with the patient aiding warming efficiency. This device is therefore particularly useful in burns patients coming to theater for change of dressings but may not convey the same benefits in prolonged open surgery. To our knowledge, this current study is the first trial directly comparing the WarmCloud with another warming device during open surgery.

Kanmed state in their advertising brochure that "Kanmed WarmCloud has been used with more than 100 000 patients. Nearly all reached 37°C core temperature."[16] There are no citations or references on the brochure to substantiate this claim, and therefore this statement must be treated with much circumspect.

It is worth reflecting on the possible reasons that the WarmCloud may not be as effective as we had hypothesized. The first, and most simple, reason for this could be that the maximum temperature of the WarmCloud is 42°C compared with the Bair Hugger, which can be turned up to 43°C. Although this 1°C difference is small, from a baseline of 36°C, this amounts to a 17% relative difference in temperature. Over 6 to 8 hours, this may make a significant clinical difference. The WarmCloud warms by conduction, so the warming effect depends on the amount of direct physical contact with the patient. By comparison, the Bair Hugger warms by convection, and in this way the actual warming mechanism, the hot air, has a large area of contact with the patient. The hot air is also constantly replaced, in contrast with the Warmcloud

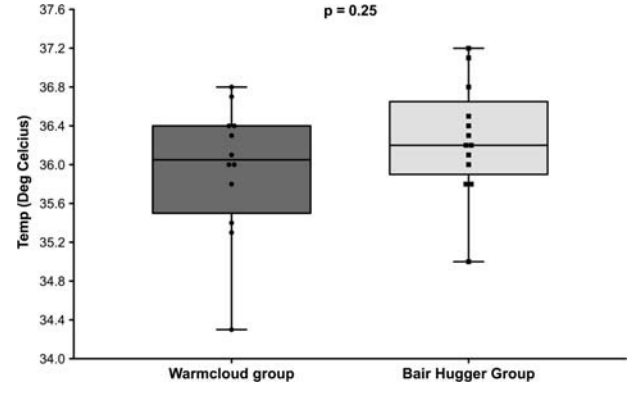

FIGURE 2. Box and Whisker plot showing participants' temperatures 5 minutes before reperfusion (primary end point) in patients undergoing OLT (*P* = 0.25).

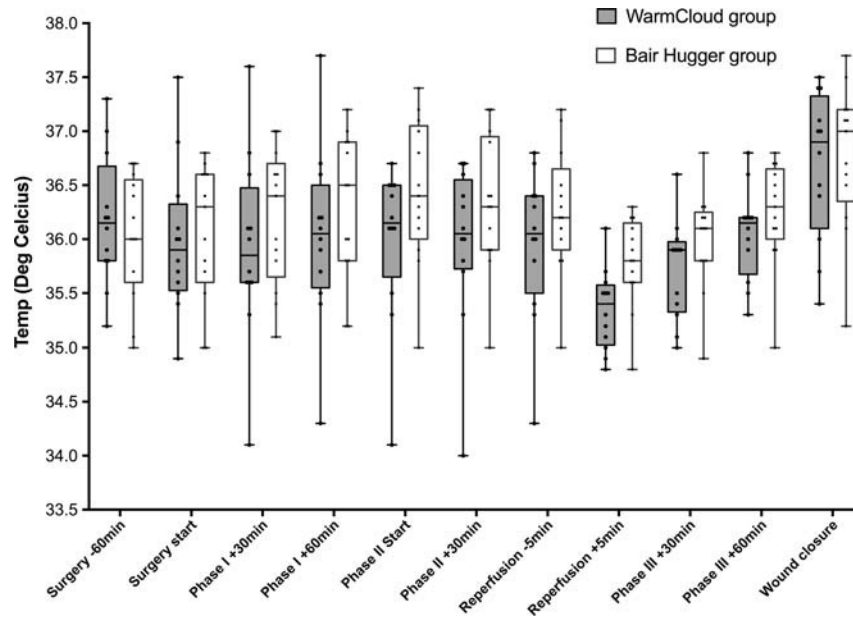

FIGURE 3. Box and Whisker plot showing changes in participants' temperatures during liver transplantation (repeated-measures ANOVA, $P = 0.25$).

where the flow of warm air replacing the air that has cooled is intermittent and therefore possibly less effective.

Although not statistically significant, more patients in the WarmCloud group reached a nadir temp below 35.5°C, and therefore had an upper body Bair Hugger added as per protocol for patient safety. This occurred in 10 patients in the WarmCloud Group and only 5 in the Bair Hugger group ($P = 0.11$), thereby confounding our study against the Bair Hugger group.

It is also worth noting that despite randomization, the duration of surgery was significantly longer and the volume of fluids administered was significantly greater in the BairHugger group. There are 3 possible explanations for these discrepancies. First, the increased duration of surgery and volume of fluid administered may be attributed to the warming devices. We do not feel that there is a plausible mechanism to account for this degree of variation. Alternately, the duration of surgery and fluids administered could have affected the resulting temperatures, potentially causing a type 2 error. A longer duration of surgery allows more time for warming making this plausible. However, any attempt to quantify this effect is fraught with error as it requires a number of assumptions. Finally, this could have been a random event and there is no association between the volume of fluids administered and the duration of surgery with core temperature. Given that we measured multiple data points, it is indeed possible that these points become significant by chance alone.

Our study had several strengths. All data points were recorded in real time and were objective, and therefore not prone to interpreter bias. The study was a randomized controlled trial and controlled for many potential confounding variables. Moreover, neither of the manufacturers of the products tested had any input into the study at any point, eliminating bias.

There were a few limitations to our study. The study was relatively small, and limited to patients undergoing OLT. Liver transplantation patients are particularly prone to hypothermia. Although the device offered no benefit to these patients, the results might not be applicable to patients undergoing other procedures. The study was also only powered to detect a difference of 0.5 degrees. The mean difference in temperature between the groups at all time points was below this, and therefore, a nonsignificant result is unsurprising.

One must also bear in mind the possibility of a type 2 error, although we feel this unlikely. With several protocol violations in a small study we sought to reanalyze the statistics adjusting for protocol violations. In all of these cases and at all endpoints, all results remained nonsignificant. We therefore concluded that the protocol violations did not significantly affect our data.

The WarmCloud has potential benefits other than maintaining normothermia. Most notably, it distributes weight very evenly which may reduce the likelihood of pressure injury. Our trial was grossly underpowered to demonstrate this potential benefit, but this feature may make it a useful product in some situations.

Given that the cost of the WarmCloud is significantly higher than the Bairhugger, with a disposable cost of $55 AUD versus $18 AUD, at the time of purchase for our trial, and it has not been demonstrated to be more effective than the BairHugger, we do not recommend the routine use of the WarmCloud device in OLT surgery outside of a clinical trial. As we did not purchase either of the base units, and the cost may vary considerably, we have not included these data.

CONCLUSIONS

When combined with standard multimodal thermoregulation strategies, the WarmCloud is comparable to the Bair Hugger at maintaining normothermia during OLT. As the WarmCloud device is a more expensive product, we cannot advocate its routine use during liver transplantation. Larger studies in this patient group should be conducted to evaluate its specific role in the prevention of pressure sores. Given the large body of conclusive evidence that surgical outcomes are better when patients remain normothermic

intraoperatively, further studies of novel warming devices are also warranted.

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