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Research Article

The Effects of Freezing on EpiPen Epinephrine Auto-Injector Device Integrity and Function

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Abstract

Background: Epinephrine Auto-Injectors (EAIs) have recommended storage temperatures between 20-25°C, with permitted excursions between 15-30°C. Prior studies suggest that freezing does not degrade epinephrine. The effect of freezing on EAIs is not well studied.

Objective: To determine the effects of freezing on EAI function and integrity.

Methods: For 109 pairs of same-dose, same-lot, post-consumer expired EpiPens (half 0.3mg, half 0.15mg), one device was frozen at -25°C for 48 hours then thawed (frozen-thawed) while its pair was kept at recommended temperatures (control). Both were then fired into meat. Paired t-tests were used to determine if the average difference in a) meat mass and b) device mass were different between frozen-thawed devices and control devices. Generalized estimating equations analyzed the paired data adjusting for device dose (0.3mg vs 0.15mg) and months expired. An additional 104 frozen and thawed unfired devices were dissected to assess for damage.

Results: In unadjusted paired comparisons, meat from frozen-thawed devices gained slightly more mass than controls during firing (0.286 vs. 0.281, paired t-test p-value=0.0075, n=104), while devices lost a similar mass (-0.284 vs. -0.28, paired t-test p-value=0.0206, n=109). In both unadjusted outcomes and the adjusted outcome for meat, there were statistically but not clinically significant increases (up to 1.8% more) in epinephrine solution fired by frozen-thawed versus control devices.

Conclusion: Freezing for 24 hours did not impair EAI device function once thawed. While freezing is not recommended, devices accidentally exposed to freezing temperatures for up to 24 hours are at low risk for malfunction.

Keywords: Foreign body; Aerodigestive tract; Radiology

INTRODUCTION

Epinephrine is the only first-line medication in anaphylaxis management and should be administered promptly when anaphylaxis is suspected [1-3]. In the community, the preferred method of epinephrine administration is an Epinephrine Auto-Injector (EAI) [3,4].The EpiPen monograph stipulates that EpiPens should be stored in the range of 20° to 25°C (68° to 77° F), with short excursions permitted between 15° and 30°C (59° and 86°F) [5].

As individuals at risk for anaphylaxis need to carry EAIs regardless of environmental conditions, devices may be exposed to much greater temperature variability than recommended [6].

While storage at excessively high temperatures can cause degradation of the epinephrine solution, [7,8] numerous studies have demonstrated the stability of epinephrine at cold and freezing temperatures [8-9]. In addition, a study of 10 EpiPens found no change in the volume fired by the devices after freezing and thawing [10]. We aim to further investigate the effects of freezing temperatures on the function and integrity of EpiPen (0.3 mg/0.3 mL epinephrine) and EpiPen Jr (0.15 mg/0.3 mL epinephrine) devices.

METHODS

Our primary aim was to determine whether EpiPen devices stored at freezing temperatures for 24 hours and then thawed (frozen-thawed) would trigger and eject epinephrine solution normally. We hypothesized that frozen-thawed EpiPens would eject the same mass of epinephrine solution as control devices. This was assessed

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by firing the frozen-thawed devices and paired control devices into meat and comparing the difference in epinephrine solution ejected between the two groups, as measured by a) change in meat mass and b) change in device mass.

EpiPen consumers (colleagues, patients and parents of children with allergies) were contacted in person and via social media and asked to donate expired EpiPen devices for this research. Expired post-consumer epinephrine auto-injector devices were paired by dose, lot number, expiration date, and consumer. For each pair, one device was frozen inside its plastic case at -25°C for 24 hours and subsequently stored at room temperature for approximately 48 hours to ensure it fully thawed. The other device of the pair remained stored within the manufacturer recommended temperature range. All frozen-thawed and paired control devices were then fired into a section of marbleized beef, used in this study to simulate human muscle tissue (Figures 1 and 2). The beef was placed in a 30 mm diameter plastic tube and covered with a double layer of latex to prevent any loss of liquid during the triggering of the device (Figure 3A).

The beef, tube and latex sample, and device were weighed pre-injection and post-injection using a Mettler-Toledo analytical balance scale with accuracy to 0.001 g (Figure 3B).

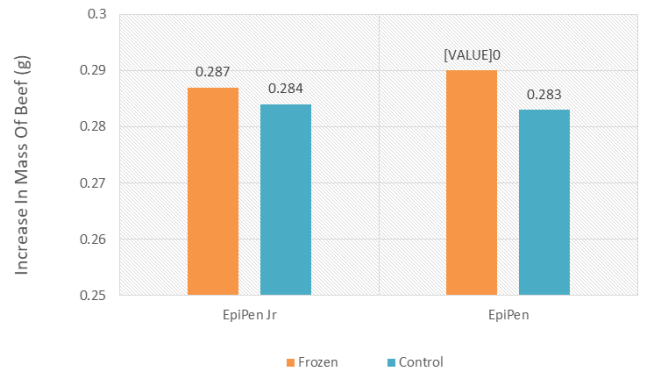

Figure 1: Average mass gained by beef during firing of EpiPen (15mg/mL and 30mg/mL) in frozen and control groups.

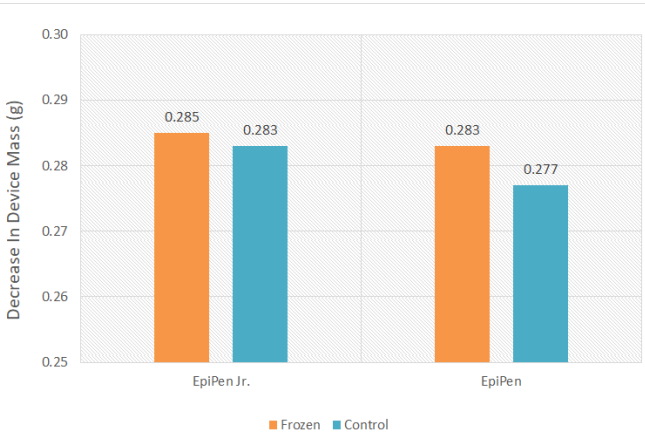

Figure 2: Average mass lost by Epipens (15mg/mL and 30mg/mL) during firing in frozen and control groups.

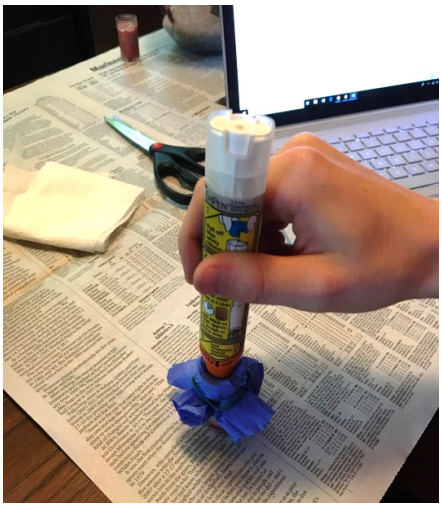

Figure 3(A): EpiPen injected into latex-sealed beef. (B) Mass of latex-sealed beef and EpiPen measured using Mettler-Toledo analytical balance scale post-firing.

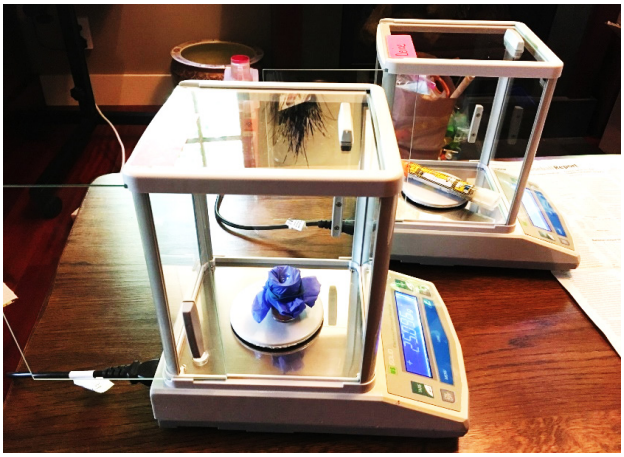

Figure 3(B): Mass of latex-sealed beef and EpiPen measured using Mettler-Toledo analytical balance scale post-firing.

The difference between pre-injection and post-injection weights of both the device and the beef were used to estimate the amount of epinephrine solution fired. The beef and latex were replaced approximately every eight triggering, once the beef became less supple. On occasions where the triggering of the device caused the container holding the meat to crack, or where solution escaped from the top of the container despite the latex seal, the container and meat were replaced and the meat weight measurements for this pair were disregarded, but the device weight measurements for the pair were still used.

The primary aim was assessed in two ways: by comparing the increase in meat mass between frozen-thawed and control devices, and by comparing the decrease in device mass between frozen-thawed and control devices. Both measures were used to estimate the mass of epinephrine solution fired. First, for a single device, the difference in mass of meat and the difference in mass of device before and after firing the device was obtained. Next, each of these differences in mass were compared between the frozen-thawed device and controls, taking into account the pairing of the frozen-thawed and control devices. Unadjusted analyses were performed using a paired t-test. Adjusted analyses were performed using

generalized estimating equations which accounted for pairing and adjusted for device dose (0.15mg vs. 0.3mg) and expiration date (in months). All statistical analyses were performed using R.

With no existing data to determine sample characteristics, the first 10 pairs tested were used to determine an appropriate sample size for this study [11]. Through calculations based on this sample we estimated that in a paired t-test, testing 22 pairs of devices would provide 90% power to detect a 5% difference in mean mass of an average control device between frozen-thawed and control measures for both the meat and device outcomes. With 109 pairs tested, we were thus adequately powered for both outcomes.

A secondary aim was to determine whether the freezing and thawing process would crack the glass epinephrine-containing vial, break the seal between the vial and needle, or otherwise damage the EpiPen device. In the initial study design, we intended to open the devices after triggering to inspect for cracked vials, broken seals or other abnormalities. In practice, we discovered that it was difficult to saw open the triggered devices without the internal springs exerting an asymmetrical pressure onto the glass vial. This pressure caused vials in both frozen-thawed and control samples to crack as the device was opened. Consequently, we modified our study design and froze and thawed an additional 104 donated devices, which were sawed open before firing, with the safety cap in place. This procedure kept the spring from being released as the device was sawed open, which allowed for an accurate assessment of the effects of freezing and thawing on the integrity of the glass syringe and other device components. The vial was carefully inspected and any cracks or defects in the glass vials were noted. The syringe plunger was gently compressed and inspected for fluid leakage, to assess for a break in the seal between the syringe and the needle.

RESULTS

There were 111 pairs of devices prepared for study, but some measurements were excluded due to technical difficulties with the analytical balance or the equipment used to contain the meat sample: 109 devices (fifty-five 0.3mg and fifty-four 0.15mg) had data for both pre- and post-firing device measurements, and 104 pairs (fifty-two 0.3mg and fifty-two 0.15mg) had data for both pre- and post-firing meat measurements.

In unadjusted paired comparisons, meat from frozen-thawed devices gained slightly more mass than controls during firing (mean mass differences: 0.286mg vs 0.281mg, paired t-test p-value=0.0075 and frozen-thawed devices lost slightly more mass versus controls when firing (mean mass differences: -0.284 mg versus -0.28 mg, paired t-test p-value=0.0206.

After adjusting for solution type and expiration date, the conclusions were unchanged (for meat outcome, adjusted difference between two arms=0.005mg, p=0.0303; for device outcome, adjusted difference between two arms=0.004 mg, p=0.055). Further interaction terms were added in the regression models between freezing and each solution type and between freezing and expiration date. Neither of the interaction terms was significant, suggesting that the effects of freezing on device function did not differ by solution type, nor expiration date. These meat mass and device mass results both found that frozen-thawed devices fired statistically or nearly statistically significantly more than control devices, but the differences detected were small and unlikely to have clinical significance. In both unadjusted and adjusted analysis, for the meat outcome the average mass increase was 1.8% more for frozen-thawed devices than control devices; for the device outcome the average mass decrease was 1.4% more for frozen-thawed devices than control devices.

When 104 untriggered frozen-thawed devices (52 of each concentration) were opened and assessed, no cracked vials or other damage was detected in any device. The rubber needle cover was in place in each device. The liquid contents could not be expressed when gentle pressure was applied, indicating that the seal between the vial and needle remained intact. We concluded that the freezing event had not impacted the integrity of any opened device. Since no damage was found in the frozen-thawed devices, the paired control devices were not examined.

DISCUSSION

In order for patients and providers to be confident that an EAI remains functional after freezing, they need assurance that both that the epinephrine compound remains stable and that the device remains intact. Numerous prior studies have demonstrated that the epinephrine compound is stable in cold and freezing conditions [12]. A systematic review of the effects of extreme temperatures on epinephrine includes evidence from 4 studies demonstrating that freezing temperatures do not degrade epinephrine [13]. In addition, one hospital-based study demonstrated that refrigeration of epinephrine ampules reduced epinephrine degradation compared with ampules stored at room temperature [14].

We found that a single 24-hour freezing event did not decrease the volume of epinephrine solution fired. While our results showed more solution fired for the frozen-thawed devices in some analyses, these statistically significant differences represented very small mass differences (≤ 0.005 mg) and small proportions (≤1.8%) of the mass fired. These differences are clinically inconsequential if the solution is uncontaminated epinephrine. They could potentially be important if the device housing had picked up condensation during the freezing-thawing process which fired as liquid along with the epinephrine, although this would be unlikely as a 48-hour period of thawing was provided which would likely allow any condensation to dissipate. In addition, there was no visible or palpable condensation on dissected frozen-thawed devices.

This study is the first investigation of EpiPen efficacy after exposure to below-freezing temperatures to include data from a large sample of EpiPen and EpiPen Jr devices, and the first study to inspect dismantled frozen-thawed EpiPens and EpiPen Jrs to assess for damage to the glass syringe and other device components. There has previously been limited evidence regarding the effects of freezing on EAI device integrity. In the only prior study involving freezing EAIs, 10 frozen and thawed EpiPens fired successfully, indicating that the device mechanisms remained intact after freezing. The frozen devices contained a volume and dose of epinephrine comparable to non-frozen controls.

Our findings that 24-hour excursions at below-zero temperatures did not negatively impact device integrity or function, along with prior research indicating that the epinephrine does not degrade at low temperatures, combine to suggest that a single freezing episode does not impair the function of EpiPen and EpiPen Jr devices. While manufacturers recommend against using an EpiPen device that has been previously frozen, [6] we believe that an EpiPen exposed to a single freezing episode is at low risk for malfunction.

It is important to note some limitations of our research. First, the frozen-thawed devices in this study were only exposed to a single 24-

hour period of freezing at -25°C. We cannot draw any conclusions regarding the effects of freezing at temperatures colder than -25°C, freezing for longer than 24 hours, or multiple freezing episodes. Secondly, although well powered for the outcome of interest, we cannot rule out the possibility of an occasional rare event affecting device integrity. Furthermore, the results of this study are specific to EpiPens and should not be generalized to other epinephrine auto-injector devices. Each brand of device has unique design and components, including substantial variation in syringe size and structure [6,7]. It remains unknown how freezing affects other types of EAIs. Finally, this study only investigated the functionality of fully thawed EpiPens. Devices fired while still partially frozen may respond differently.

For convenience of access, our study used post-consumer expired EpiPen devices. Because EpiPen devices are sold in pairs, and because devices remain paired when in the possession of a consumer, we assume that both devices in each pair experienced equivalent environmental conditions, including temperature, humidity, and exposure to light. The paired study design controlled for these variables, as well as expiration date. Although we observed differences in the volume of epinephrine solution fired based on the expiration date, with longer-expired EpiPens firing less epinephrine solution than more recently expired devices, pairing accounted for these differences when evaluating the effect of freezing, our outcome of interest. Because we accounted for expiration date using this paired design, and did not find any damage to the frozen-thawed devices on dissection, we do not believe our results differed from what we would have obtained had we used unexpired devices.

CONCLUSION

Freezing for 24 hours did not impair EpiPen or EpiPen Jr device function once thawed. Frozen-thawed EpiPen and EpiPen Jr devices ejected at least an equivalent mass of solution to their control device pairs stored at room temperature. EpiPen and EpiPen Jr devices remained intact despite freezing, with no evidence of cracked vials, broken seals, or other damage. We therefore conclude that while freezing is not recommended, an EpiPen accidentally frozen once for a short period of time appears to be at low risk for malfunction.

CONFLICT OF INTEREST

None.

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