CryoPop

Enabling Affordable Prevention of Cervical Cancer in Developing Countries

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Background/Clinical Problem:

Cervical Cancer *Kills* more than 250,000 women annually

- More than 85% of cases occur in developing nations where a lack of healthcare infrastructure prohibits the developed world care model to be directly implemented
- Cervical cancer develops slowly and without symptoms over the course of approximately one decade
  - Precancerous lesion growth is initiated by HPV infection and progresses until it becomes a morbid and untreatable condition
- In the developed world there is healthcare and governmental infrastructure to support, the trained physicians, pathologists, pathology labs, and information systems required to screen and appropriately treat women (however this is expensive, the US spends more than $6 billion/year just observing benign lesions[1])

Figure 1: Dramatic infrastructural differences lead to the disproportionately high cervical cancer incidence rates in developing countries (highest incidence rates are shown in red and dark orange on the map)

Visual Inspection with Acetic Acid (VIA) can provide immediate diagnosis but it needs to be coupled with an appropriate treatment method that can be performed in Rural Health Posts in order to effectively reduce cervical cancer incidence

- Costs approximately $0.05 per woman screened
- Is performed by a trained nurse or midwife
- Provides instant diagnosis of pre-cancerous lesions
- Requires only vinegar, cotton swabs, speculum, and a light source (flashlight)
- Does NOT require a pathologist; who may not even exist in the country
- Proven to be 79-84%[2-4] sensitive (Pap Smear is only 51-68%[5-7])
- No benefit to screening if there is no treatment available because women will not journey to the district hospital to seek follow-up care

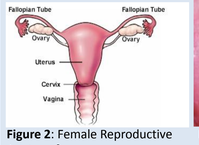

Figure 2: Female Reproductive Anatomy[8]

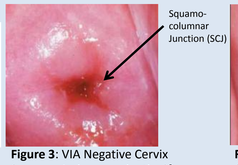

Figure 3: VIA Negative Cervix (as seen during examination)[9]

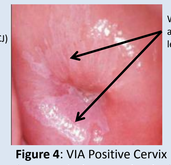

Figure 4: VIA Positive Cervix (as seen during examination)[9]

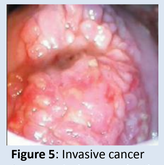

Figure 5: Invasive cancer (as seen during examination)[9]

Figure 7[10]: Jhpiego was the pioneer for VIA in the early 1990s and is currently active in over 60 developing countries (shown in green) specializing in training and distribution of appropriate health technologies; Jhpiego presented this need to CBID in Fall of 2011

Cryotherapy has the potential to be coupled with VIA to provide an effective treatment option for precancerous lesions in rural Health Posts around the developing world

- Cryotherapy simply freezes the entire surface of the cervix destroying both healthy and pre-cancerous cells; after the therapy only healthy cervical cells regenerate
- Can be effectively performed by a trained nurse or midwife (78.0% - 92.6% effective depending on lesion grade and size[11])
- Very low risk of complications, 1-4% minor complications, <.03% major complications requiring hospital interventions[12]
- Can be performed without anesthesia
- Clear indications for cryotherapy:
  - Lesion covers less than 75% of the cervix
  - Lesion does not extend into the endocervical canal
  - No suspicion of invasive cancer
- Re-treatment is an option for those lesions which are not treated the first time
- CO_2 readily available in all developing countries due to the presence of soda companies

Need:

"There is a great need to improve cryotherapy methods, especially those based on CO_2, for treatment of cervical precancer in resource-poor countries, where electrosurgical removal of the transformation zone is largely unavailable."[13]

Current cryotherapy equipment is not designed for the developing world and is plagued by its 30 year old design which manufacturers are unwilling to update because of a perceived lack of business profitability

- Expansion of compressed gas occurs right at the cryoprobe tip cooling the tip surface to between -56°C (with CO_2) and -69°C (with N_2O)[16]
- Equipment was designed over 30 years ago for use with N_2O in the developed world
- When used with CO_2 there is a high chance of blockages due to moisture and particulate clogging up the fine internal tubing, resulting in warmer tip temperatures reducing the efficacy of the treatment
- Not considered durable and repair knowledge in the field is minimal
- Costs approximately $2000, additional cryotips (which are prone to corrosion during disinfection) cost roughly $300
- Inefficient with CO_2, a single 50lb tank can only treat 10 women
  - Difficult to transport a 50lb tank to the rural health posts where the technology is most needed

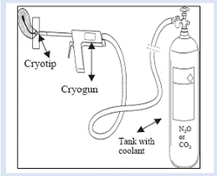

Figure 8: Existing cryotherapy set-up[14]

Figure 9: Cryotherapy probes: can be flat or convex to self locate (note the plastic disposable shields)[15]

The LL100's internal tubing consists of 3 different diameter tubes hand brazed together, a time consuming and labor intensive process

The LLCO2/Leisegang model has a simpler internal set of tubing but requires individual calibration of each individual unit with a specific tip, also a labor intensive process

Figure 10: Hand crafted internal tubing is difficult to manufacture and is prone to clogging, bending, and breaking

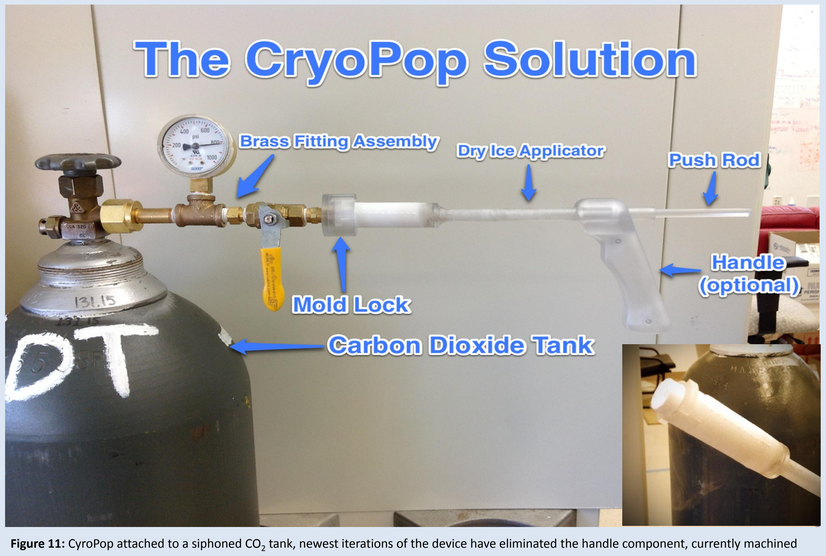

Figure 11: CyroPop attached to a siphoned CO_2 tank, newest iterations of the device have eliminated the handle component, currently machined

Capitalizes on the liquid portion of the CO_2 within the pressurized cylinder to create dry ice consistently and efficiently

- Expansion of liquid CO_2 creates dry-ice (always at -78°C when it is ice)
- Reduced variability in tip temperature, user can tell if there is no dry ice
- Assembly of only 4 primary injection molded components and 3 standard brass fittings
- Easily disassembled and sterilized or disinfected (HLD) in chlorine
- Expected selling price of $200
- No disposables or expensive corrosion prone tips

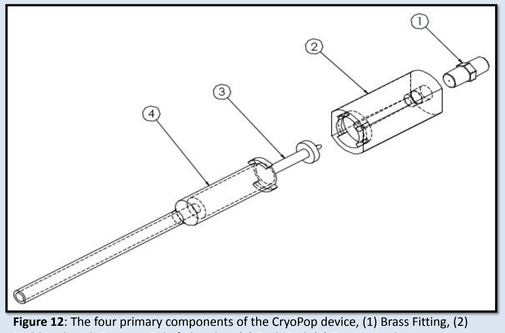

Figure 12: The four primary components of the CryoPop device, (1) Brass Fitting, (2) Mold Lock with Pressure Relief Chamber, (3) Push Rod, (4) Dry Ice Applicator

Testing Conducted:

The CryoPop has been tested on the bench and in animals to show that it is at least as effective as the current standard of care and it is also safe for both the patient and the user

Bench Performance Testing

- Compared the CryoPop against the Wallach LL100 using a similar test setup to the protocol of Seamans et al. in 2007 to evaluate the effect of the "cough technique"[16]
- Turkey breast cut to 30mmx30mmx15mm and thermocouple implanted 5mm deep

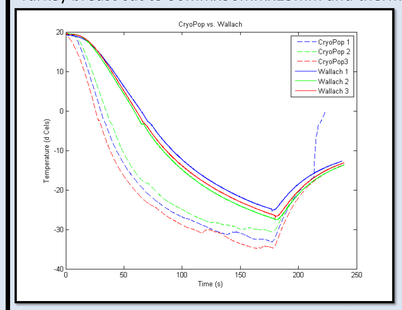

Figure 13: Small sample runs comparing the temperature of the turkey breast at 5mm deep between the Wallach LL100 and the CryoPop (25 mm flat tip used and compared against a 25mm diameter CryoPop)

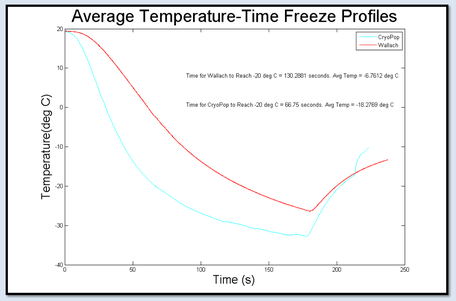

Figure 14: Average values (from Figure 13) compared between the Wallach and the CryoPop, faster time to -20°C and lower average temperature indicate that the CryoPop will result in more extensive necrosis and result in better patient outcomes

Bench Fill Testing

- A single 5lb tank can produce enough dry ice to ablate 30 patients (360g)
- Designed the mold lock to enable pressure drop before filling the Dry-Ice Applicator enabling more consistent filling without air pockets
- Found that additional compression needs to take place after the filling in order to create the right density of ice (roughly 0.9g/cm^3)

Animal Testing:

- Performed cryoablation on 6 goat cervixes: 3 with the Wallach LL100 and 3 with the CryoPop
- Goats were old and their cervixes had begun to recede similar to post-menopausal women
- Gross pathology is hard to interpret but appears to be comparable between the two devices
- Histology revealed no necrosis, only edema; need to wait longer than 24hrs before harvest to enable necrosis to occur

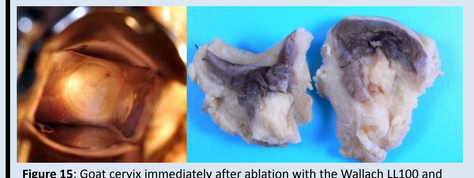

Figure 15: Goat cervix immediately after ablation with the Wallach LL100 and after harvest (fixed in formalin)

Figure 16: Goat cervix immediately after ablation with the CryoPop and after harvest (fixed in formalin)

Conclusion: A proven technology that has the potential to save hundreds of thousands of lives around the developing world

The CryoPop achieves lower freezing temperatures than existing cryotherapy equipment

The CryoPop costs 1/10 of what existing cryotherapy costs

The CryoPop is 30 times more efficient with the expensive but readily available CO_2

The CryoPop is more durable and reliable than the existing cryotherapy units

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