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Review

The effect of introducing point-of-care or dried blood spot analysis on the uptake of hepatitis C virus testing in high-risk populations: A systematic review of the literature

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ABSTRACT

Background: Testing for hepatitis C virus (HCV) infection typically relies upon blood samples taken by traditional phlebotomy for laboratory processing. Novel testing methods, including using dried blood spots (DBS) and point-of-care (PoC) testing enable easier access to high risk populations who have less frequent contact with healthcare professionals. Many of these individuals have been exposed to HCV but have not previously been tested. We aimed to establish whether the availability of these novel testing methods increased either uptake of testing or the number of new diagnoses of HCV.

Methods: The PubMed, Cochrane and SCOPUS databases were searched for terms relating to the study. References and associated bibliographies were also examined for further relevant articles. Studies were included if they contained quantitative data on frequency of testing and/or new diagnoses following the introduction of PoC and/or DBS testing of high-risk populations. Studies were then examined for findings and limitations and graded upon the quality of evidence provided.

Results: No studies were found which introduced PoC testing and determined its effect on frequency of testing or new diagnoses. Six studies were identified in which DBS testing was introduced and its effect evaluated. Two of the studies were randomised controlled trials, two were prospective cohort studies, one was an ecological study and one was a clinical audit. Populations studied included those attending substance misuse clinics, prisons and needle exchanges. Injection drug use was the commonest risk factor for HCV. Five of the six studies provided evidence that the introduction of DBS testing increased the number of tests, new diagnoses or both.

Conclusion: Current evidence indicates that DBS testing availability may increase the uptake of testing for HCV in high-risk populations. There is currently no evidence regarding the efficacy of PoC testing in these populations.

Introduction

Hepatitis C virus (HCV) is a common hepatotropic flavivirus which has infected more than 170 million people worldwide (De Francesco & Migliaccio, 2005). It leads to chronic infection in around 75% of those exposed and may progress to liver cirrhosis and hepatocellular carcinoma (Donato et al., 2002; Micallef, Kaldor, & Dore, 2006; Wiese, Berr, Lafrenz, Porst, & Oesen, 2000). Infection in the developed world occurs most commonly following blood-to-blood contact, often due to needle sharing among people who inject drugs (PWID) but can also occur following sexual contact or the use of contaminated blood products (Shepard, Finelli, & Alter, 2005).

HCV prevention strategies involving the introduction of needle exchange programmes for PWID along with increasing the availability of opioid substitution therapy (OST) have become widespread. Until recently there was limited evidence regarding the efficacy of these interventions but evidence now indicates that coordinated programmes can lead to a reduction in HCV incidence (Palmateer et al., 2014; White, Dore, Lloyd, Rawlinson, & Maher, 2014).

HCV can be successfully treated with antiviral therapy. Previously this involved prolonged courses of pegylated interferon alpha and ribavirin but recent clinical trials have now provided evidence of improved efficacy with interferon-sparing all-oral antiviral therapy (Chung & Baumert, 2014). Evidence obtained from mathematical models indicates that a dramatic reduction in

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the incidence of HCV would be obtained by increasing the numbers of PWID being treated (Martin et al., 2011; Martin, Hickman, Hutchinson, Goldberg, & Vickerman, 2013; Martin, Vickerman et al., 2013). By reducing the pool of high risk individuals with HCV the transmission of infection would theoretically also be reduced; however this relies upon good case finding of which diagnostic tests are a vital component.

Guidance on when and who to test for HCV infection has been updated in recent years in an attempt to identify asymptomatic individuals who are infected and who require treatment prior to the development of complications. The Centres for Disease Control (CDC) produced guidelines in 2012 recommending one-off testing of the entire US population born between 1945 and 1965 (Smith et al., 2012). Although the prevalence of HCV infection in this group is likely to be low, estimated at 2.6%, screening such a large cohort is likely to identify a significant number of people unaware that they are chronically infected with HCV and who are at risk from the longterm sequelae of infection (Denniston et al., 2014). The Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) additionally recommend annual testing for men who have sex with men who are known to be infected with HIV, as well as PWID (AASLD, 2014).

The current initial diagnostic test for HCV infection relies upon the detection of HCV antibodies (anti-HCV) by enzyme linked immunoassays (EIA). These have undergone multiple generations of development with current kits utilising many antigens to improve sensitivity; the core, NS3, NS4 and NS5 (Barrera et al., 1995). This has enabled earlier detection of infections by reducing the time window from initial infection to test positivity. The window period is variable between individuals but has reduced from around 16 weeks with first generation testing, to 10 weeks with second generation and 2–3 weeks with third generation testing (Gretch, 1997).

A positive anti-HCV test indicates that the person may be actively infected, have spontaneously cleared the infection or the result may be a false positive. Previously a subsequent more specific antibody test, the Chiron RIBA immunblot assay, was used to verify samples reactive for anti-HCV but this is no longer available (Centers for Disease and Prevention, 2013). Therefore nucleic acid testing for HCV RNA is now standard of care (Centers for Disease and Prevention, 2013).

Whilst the detection of anti-HCV antibodies by EIA represents the gold standard to which novel testing methods should be compared it does have limitations, particularly in populations of PWID. The method typically requires venepuncture for serum analysis in a specialist laboratory which relies upon client contact with trained healthcare professionals. There are many studied barriers to the treatment of HCV in PWID; those related to initial diagnosis include system referral delays and clients missing appointments (Morrill, Shrestha, & Grant, 2005). Even when such barriers are overcome there may be practical difficulties with venepuncture limiting the availability of testing (Mason, Watts, Sheils, & Koorey, 2007). Standard EIA testing also necessitates a delay between testing and results, thereby requiring the client to return to receive their results.

Novel testing methods which enable easier case-finding and testing by non-healthcare professionals, and those not trained in venepuncture, are now available. These novel methods include dried blood spot (DBS) testing and rapid detection of anti-HCV antibody using point of care (PoC) kits.

DBS testing involves fingertip capillary sampling to provide a drop of blood. This is then spotted onto specialist filter paper which enables comparatively non-invasive sampling and easy storage. The paper can then be analysed for both anti-HCV antibody and, more recently, HCV RNA, thereby potentially circumventing the requirement for traditional phlebotomy which can be particularly problematic in PWID. The DBS testing of both antibody and RNA has been found to perform well when compared to traditional diagnostic methods. Indeed the DBS EIA has sensitivity and specificity approaching 100% (Bennett et al., 2012; Dokubo et al., 2014; Judd et al., 2003). The DBS test process is non-technical in comparison to phlebotomy and can be carried out by non-healthcare professionals thus broadening its use to non-traditional settings which may include needle exchanges, substance misuse clinics and prisons (Bennett et al., 2012).

Rapid immunochromatographic assays for the detection of anti-HCV antibody are also available, these produce a result in a short period of time enabling point-of-care testing (PoC). This test also requires no traditional phlebotomy and potentially reduces the number of appointments which must be attended before diagnosis and treatment could be initiated. The first to be licensed, the OraQuick HCV Rapid Antibody Test (OraSure Technologies) was approved by the CDC in the USA in 2011. These rapid PoC tests have been found to have high sensitivity and specificity, particularly if blood is used rather than oral fluid (Shivkumar, Peeling, Jafari, Joseph, & Pant Pai, 2012).

This systematic review aimed to identify whether the introduction of PoC or DBS testing increased the frequency of testing or number of new diagnoses of HCV infection in high risk populations including PWID.

Methods

The PubMed, SCOPUS and Cochrane databases were searched for the following terms: "Hepatitis C" OR "HCV" AND "dried blood spot" as well as "Hepatitis C" OR "HCV" AND "point of care" OR "rapid test." The results were limited to studies in English which were published between 2004 and November 2014. References and associated bibliographies were also examined for further relevant articles.

The population of interest were those individuals reporting previous or current injection drug use, prison populations and those attending substance misuse or needle exchange programmes. Studies in which only a proportion of the total number tested was high risk were also included with this limitation noted. The interventions examined were either DBS or rapid immunochromatographic PoC testing offered as a means of testing for HCV. For the purposes of this review only rapid immunochromatographic assays were regarded as PoC testing as results are provided in minutes without the requirement for laboratory processing. Standard EIA anti-HCV testing with rapid result turnaround and DBS were not deemed to be truly PoC. Studies with and without a control or comparison group were included. The outcomes examined were quantitative evidence of test uptake and frequency of new diagnoses of HCV. Studies of all types were included.

A single reviewer performed the initial search with two reviewers examining abstracts and full text articles. Data was extracted to standardised tables. Studies were examined for findings and limitations and graded upon the quality of evidence provided using the Scottish Intercollegiate Guidelines Network (SIGN) method of assessing trials (SIGN, 2011).

Results

Search results and inclusion of studies

2619 results were identified from the search of the PubMed, SCOPUS and Cochrane databases. The titles and abstracts of these were then examined for potential relevance. 15 studies were then manually reviewed in their entirety for relevance to this review of which 5 met the inclusion criteria. A single other relevant study