Venous access devices for the delivery of long-term chemotherapy: the CAVA three-arm RCT

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Scientific summary

The CAVA three-arm RCT

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Scientific summary

Background

Venous access devices are used for patients receiving long-term chemotherapy. These include centrally inserted tunnelled catheters or Hickman-type devices (Hickman), peripherally inserted central catheters and centrally inserted totally implantable venous access device (PORTs). It is unclear which is the best device from an efficacy, a safety and a health economics perspective.

Objectives

The specific objectives were to determine:

- whether or not peripherally inserted central catheters are non-inferior to Hickman with regard to complication rates
- whether or not PORTs are superior to Hickman with regard to complication rates
- whether or not PORTs are superior to peripherally inserted central catheters with regard to complication rates
- the cost-effectiveness of Hickman, peripherally inserted central catheters and PORTs
- the acceptability of Hickman, peripherally inserted central catheters and PORTs to patients and clinical staff.

Methods

An open, multicentre, randomised controlled trial of the three devices was undertaken in adult patients (aged $\geq$ 18 years) receiving chemotherapy (minimum duration of 12 weeks) for either a solid or a haematological malignancy. Four randomised options were available: (1) Hickman versus peripherally inserted central catheters versus PORTs, (2) peripherally inserted central catheters versus Hickman, (3) PORTs versus Hickman and (4) PORTs versus peripherally inserted central catheters. These patients formed the basis of the three comparisons: (1) peripherally inserted central catheters versus Hickman, (2) PORTs versus Hickman and (3) PORTs versus peripherally inserted central catheters. Following device insertion, patients were monitored until the device was removed (up to a period of 12 months). Pre- and post-trial qualitative studies using patient focus groups and staff interviews were conducted to explore views about participation in the trial and the acceptability of the three devices. An economic evaluation was performed from the perspective of the NHS to determine the cost-effectiveness. Statistical analysis and within-trial cost-effectiveness analysis were performed for each of the three comparisons.

Outcome measures

The primary end point was complication rate, a composite of the inability to aspirate blood, venous thrombosis, pulmonary embolism related to the device, infection associated with the device (suspected, confirmed or exit site), mechanical failure (line fracture, line separation from the chest wall port, exposure of the line cuff, exposure of the chest wall port or breakdown of the wound, chest wall port flip, line fallen out or line migration requiring intervention) and other complications. Secondary outcomes included incidence of individual complications, complications per catheter-week, time to first complication and duration of chemotherapy treatment interruptions. Quality of life was assessed using the EuroQoL-5 Dimensions, three-level version, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, and a study-specific Venous Access Device Questionnaire.

Results

Peripherally inserted central catheters versus Hickman

Similar overall complication rates were reported across the two arms (52% with peripherally inserted central catheters and 49% with Hickman). However, it could not be concluded that peripherally inserted central catheters were significantly non-inferior to Hickman in terms of complication rate (odds ratio 1.15, 95% confidence interval 0.78 to 1.71). Overall, peripherally inserted central catheters were in situ for a shorter duration than Hickman (with a difference in median of 25 days). When this was taken into account, peripherally inserted central catheters were found to be associated with higher rates of complications per catheter-week (0.12 ± 0.02 complications) than Hickman (0.07 ± 0.01 complications). Device removal as a result of complications was common in both arms (42% of patients in the peripherally inserted central catheters arm and 32% of patients in the Hickman arm). Peripherally inserted central catheters were associated with higher rates of an inability to aspirate blood (21% peripherally inserted central catheters vs. 16% Hickman) and mechanical failure (11% peripherally inserted central catheters vs. 8% Hickman) than Hickman. By contrast, Hickman was associated with higher rates of all types of infections than peripherally inserted central catheters (11.3% peripherally inserted central catheters vs. 37% Hickman). Similar rates of venous thrombosis, pulmonary embolism and other complications were reported. Venous thrombosis was uncommon (6% peripherally inserted central catheters vs. 5% Hickman). There was no significant difference in quality of life as measured by the EuroQoL-5 Dimensions or the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30. The device-specific quality-of-life instrument did show a significant benefit in favour of Hickman for 2 of the 16 questions (i.e. hygiene and hobbies), but this significance was lost when adjusted for multiple testing. The use of peripherally inserted central catheters was associated with a substantially lower cost (–£1553) and decrement in quality-adjusted life-years gained (–0.009) than the use of Hickman; the difference in quality-adjusted life-years gained was not statistically significant. Compared with Hickman, peripherally inserted central catheters were associated with an incremental cost-effectiveness ratio of £172,556 saved per quality-adjusted life-year lost and, based on a cost-effectiveness ceiling ratio of £20,000, a net monetary benefit of £1373.

PORTs versus Hickman

PORTs were found to be statistically significantly superior to Hickman in terms of complication rate (odds ratio 0.54, 95% confidence interval 0.37 to 0.77). Overall, PORTs were in situ for a substantially longer period than Hickman (with a difference in median of 202 days). When this was taken into account, PORTs were found to be associated with 0.02 ± 0.00 complications per catheter-week, compared with 0.06 ± 0.01 complications per catheter-week in the Hickman arm. Device removal as a result of complications was far less frequent in the PORTs arm (14%) than in the Hickman arm (32%). Both arms reported similar rates of the inability to aspirate blood (15% PORTs vs. 14% Hickman) and other complications (5% PORTs vs. 6% Hickman). PORTs were associated with substantially lower rates of laboratory-confirmed bloodstream infection (5% PORTs vs. 16% Hickman), exit site infection (4% PORTs vs. 9% Hickman) and mechanical failure (0.8% PORTs vs. 3% Hickman) than Hickman. However, suspected catheter-related bloodstream infection was slightly higher in the PORTs arm (8%) than in the Hickman arm (5%). Venous thrombosis was rare and was reported in 1% of the patients in the PORTs and in 2% of patients in the Hickman arm. We found no significant difference in the quality of life as measured by the EuroQoL-5 Dimensions or the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30. By contrast, the device-specific quality-of-life instrument did show a significant benefit in favour of PORTs for 11 of the 16 questions. PORTs were associated with lower cost than Hickman (–£45) and a small increment in quality-adjusted life-years gained (0.004). PORTs dominate Hickman. This was alongside a lower complications rate (difference of 14%), resulting in an incremental cost of £1.36 per complication averted. Compared with Hickman, PORTs were associated with an incremental cost-effectiveness ratio of –£11,250 per quality-adjusted life-year gained (note that a negative incremental cost-effectiveness ratio in this case was because PORTs were dominant) and, based on a cost-effectiveness ceiling ratio of £20,000, a net monetary benefit of £125.

PORTs versus peripherally inserted central catheters

PORTs were found to be statistically significantly superior to peripherally inserted central catheters in terms of complication rate (odds ratio 0.52, 95% confidence interval 0.33 to 0.83). Overall, PORTs were in situ for a substantially longer period than peripherally inserted central catheters (difference in median of 274 days). When this was taken into account, PORTs were found to be associated with 0.05 ± 0.02 complications per catheter-week, compared with 0.13 ± 0.02 complications per catheter-week in the peripherally inserted central catheters arm. Device removal as a result of complications was less frequent in the PORTs arm (24%) than in the peripherally inserted central catheters arm (38%). The PORTs arm was associated with a lower rate of the inability to aspirate blood (16%) than the peripherally inserted central catheters arm (19%). Although infection rates (any type) were reported in a greater proportion of PORTs patients than in peripherally inserted central catheters patients (12% of PORTs patients vs. 8% of peripherally inserted central catheters patients), the mean number of infections per catheter-week was similar when device time in situ was taken into account (0.02 infections in both arms; data not shown). Venous thrombosis was reported in 2% of patients in the PORTs arm compared with 11% of patients in the peripherally inserted central catheters arm; this difference in complication rates was statistically significant. Mechanical failure was reported in 3% of patients in the PORTs arm, compared with 11% of patients in the peripherally inserted central catheters arm. We found no significant difference in the quality of life as measured by the EuroQoL-5 Dimensions or the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30. By contrast, the device-specific quality-of-life instrument did show a significant benefit in favour of PORTs for 8 of the 16 questions. PORTs were associated with an incremental cost of £1665 when compared with peripherally inserted central catheters, and a small decrement in quality-adjusted life-years gained (–0.018); this difference in quality-adjusted life-years was not statistically significant. PORTs are dominated by peripherally inserted central catheters. However, this was alongside a lower complications rate (difference of 15%), resulting in an incremental cost of £104 per complication averted. Compared with peripherally inserted central catheters, PORTs were associated with an incremental cost-effectiveness ratio of –£56 per quality-adjusted life-year gained (note that a negative incremental cost-effectiveness ratio in this case was because PORTs were dominated) and, based on a cost-effectiveness ceiling ratio of £20,000, a net monetary benefit of –£2025.

Qualitative study

The pre-trial qualitative study identified a number of issues (e.g. logistics and complexity of service delivery, need for education and training, and lack of equipoise) that had the potential to present significant barriers to recruitment. As a result, the remit of the role of the Cancer and Venous Access (CAVA) champion was developed to encompass not only recruitment and randomisation, but also co-ordination and facilitation of device insertion appointments, communication and liaison across specialties, and education and dissemination of knowledge. Effective training models and manikins were also shared between centres, and additional meetings between the chief investigator and haematologists were undertaken to address issues around equipoise. The post-trial qualitative work showed that, although all three devices presented challenges for staff and patients, all three were regarded as acceptable and preferable to peripheral cannulation. PORTs were acknowledged to be more challenging from a clinical and management perspective; however, clinical staff favoured them because they were seen as being better for patients. Indeed, staff were very well-attuned to patient experiences and cited the same practical conveniences of PORTs, as well as the emotional and psychological benefits of a less conspicuous or obtrusive device that patients themselves raised.

Limitations

The change in landscape of clinical practice over the duration of the CAVA trial had an impact on recruitment to the trial. Peripherally inserted central catheters were becoming the preferred option to Hickman. This resulted in under-recruitment to one of the three comparisons (peripherally inserted central catheters vs. Hickman) and, subsequently, a lack of adequate power (64%) in the non-inferiority comparison between the two devices.

The CAVA trial was pragmatic in nature. There was heterogeneity in how these devices were placed and managed. This, coupled with a possible learning curve with use of PORTs in many centres, may have led to higher than expected complications rates. There was also heterogeneity among the patient population, specifically the inclusion of patients with solid tumours and haematological malignancies. Patients with haematological malignancies constituted only a very small proportion of the CAVA trial population, but, among these patients, high infection rates were observed. However, we did not have sufficient data to draw firm conclusions on this subpopulation.

Conclusions

PORTS appear a better option for most patients based on a lower complication rate than the other two devices. The device-specific quality-of-life questionnaire showed significant differences in favour of PORTs, which were also supported by the post-trial qualitative research. The health economic benefits of PORTs were less clear from the perspective of quality-adjusted life-years gained; neither the EuroQoL-5 Dimensions nor the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 instruments were sensitive to any of the device-related complications. However, dependent on the willingness to pay, PORTs may be considered cost-effective from the perspective of complications averted. Peripherally inserted central catheters should be considered a cost-effective option when compared with Hickman.

Future work

The deliverability of a PORTs service merits further study to understand the barriers to and methods of improving the service. In addition, efforts should be directed to reducing this cost before widespread adoption can be recommended. Attention should be focused on the extension of the role of the peripherally inserted central catheter nursing groups to include Hickman and PORTs. There are several centres that have developed successful delivery models where this has worked. There is an urgent need for an agreed protocol on the choice, placement and maintenance of these devices. Furthermore, it is worth exploring the value of PORTs in other indications such as computerised tomography contrast imaging, parenteral nutrition and renal dialysis.

Trial registration

This trial is registered as ISRCTN44504648.

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