Original Article

Deviation in the predefined calibration factors of the dose calibrators and the associated inaccuracy in the radioactivity measurements of beta-gamma emitters

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ABSTRACT

Aim: To determine whether the predefined calibration factors of the dose calibrators can provide accurate radioactivity measurements of beta-gamma emitters used in routine therapeutic nuclear medicine procedures. **Materials and Methods:** Two models of dose calibrators were used in the present study for radioactivity measurements of ^{153}Sm ethylenediamine-N, N, N′, N′-tetrakis methylene phosphonic acid (EDTMP) and ^{177}Lu (EDTMP). A known (precalibrated) activity of each of the two beta emitters received by us from our National Supplier for administration to the patients with extensive bony metastases for bone pain palliation, was used for experiments. **Results:** When we used the manufacturers' provided dial setting of 450 × 10, each of the dose calibrators underestimated the radioactivity of ^{177}Lu by about 9.0%. Dial settings of 403 × 10 and 408 × 10 for ^{177}Lu on CRC-15R and CRC-ultra dose calibrators respectively were calculated experimentally using an iterative approach. The radioactivity measurements made at these settings provided an excellent agreement with the specified values. Likewise, a dial setting of 230 for each of the two dose calibrators was calculated for ^{153}Sm, which provided a good agreement between the experimentally derived radioactivity values and the certified values. A deviation of ± 5.0% was observed when radioactivity of ^{177}Lu and ^{153}Sm was measured over a wide range (4.0 MBq to 2.1 GBq) for time intervals equivalent to 4.5 half-lives of each of the two radionuclides. A deviation of ± 5% was observed when radioactivity was counted in different dilution volumes and in syringes of varying size. **Conclusion:** These variations could lead to a cumulative error of about 20.0% toward the inaccuracy in the radioactivity measurements of the beta-gamma emitters and thus predefined calibration factors of the dose calibrators may require experimental re-setting of these parameters and periodic checking to provide accurate radioactivity estimates of beta-gamma emitters in a given clinical setting.

Keywords: Beta-gamma emitter, calibration factor, dose calibrator, lutetium-177, samarium-153

INTRODUCTION

Beta emitters that selectively concentrate at the bone metastatic sites deliver a radiation dose adequate for relieving bone pain in cancer patients.[1] The manufacturers of the dose calibrators generally provide calibration factors/settings, which provide adequate accuracy in radioactivity measurements for commonly used gamma and positron emitters. Although the calibration factors for glass vials and syringes may not differ significantly for γ-emitters, yet difference of about 10.0% each have been reported for gallium-67 and thallium-201 measurements.[2] Likewise, an error of about 10.0% has been reported in the accuracy of these factors for the dose measurement of positron emitters and approximately 30% error for rhenium-188.[3,4]

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The sensitivity of dose calibrators for beta emitters is generally low as these radiations are absorbed in the radioactive solution itself or in the walls of the vial/syringe and the absolute method to measure betas using 4π geometry. The later leads to the production of bremsstrahlung radiations and only a small fraction of these radiations are actually detected as most of these low energy radiations are attenuated. Further,

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the amount of these bremsstrahlung radiations depends on the atomic number of the radionuclide (s) from which they are produced.[5]

The dose of these beta emitters used for achieving bone pain palliation is much lower than that used for the therapeutic purpose and there is a very narrow dose window for the observed "optimal" - pain palliation and the "side effects" of bone marrow suppression.[6,7] Therefore, an accurate dose measurement of beta emitters is required to achieve the desired therapeutic efficacy and for the best clinical outcome.[8-10] Although some manufacturers of the dose calibrators claim high accuracy and reproducibility for the radioactivity measurements of beta emitters, yet few studies have reported variations in these parameters.[11] Therefore, the present study was performed to evaluate deviation, if any, in the experimental values from the predefined calibration factors of the dose calibrators in order to calculate the associated inaccuracy in the radioactivity measurements of two (samarium-153 [^{153}Sm] and lutetium-177 [^{177}Lu]) beta-gamma emitters in our laboratory. The effect of geometric variations on the evaluation of these parameters by dose calibrators was also studied.

MATERIALS AND METHODS

Two dose calibrators (CRC-15R and CRC-ultra, Capintec Inc., Ramsey, NJ, USA) based on ionization chamber packed with a high-pressure argon as detector were used in the present study. To check calibrator stability, daily measurements were carried out using high-stability check source of cesium-137 (7.74 MBq; RadQual, New Hampshire, USA). A known amount of radioactivity of samarium-153 ethylenediamine-N, N, N', N'-tetrakis methylene phosphonic acid (^{153}Sm-EDTMP) and lutetium-177 EDTMP (^{177}Lu-EDTMP), certified and supplied by BRIT, BARC, Mumbai, India with each consignment of the therapeutic dose of these radio-nuclides was used for the purpose of calibration of dose calibrators. The isotopic characteristics of Sm-153 and Lu-177 are given in Table 1.[12] Radioactivity measurements were made by placing the vial in the reference position as shown in Figure 1a.

Determination of dial setting number for dose calibrator

The calibration factors/dial settings of the dose calibrators (CRC-15R and CRC-ultra) for ^{153}Sm and ^{177}Lu were determined using the following equation:

$$R_c = (N_c/1075.8) + 0.0797 \qquad (1)$$

Where N_c is the calibration setting and R_c is the response factor for the corresponding channel C. This expression is described in the service manual.[13,14]

A linearity test for the calibrator response was performed by measuring the given radioactivity of ^{153}Sm and ^{177}Lu solutions at different times on the determined dial setting number. The decay corrected experimental values of the measured radioactivity were plotted as a function of half-life (time) using a semi-log scale. The experimental values were subjected to an appropriate statistical analysis.[15]

Determination of effect of geometric variations on calibration factors

Syringes (Dispovan, Hindustan Syringes and Medical devices Ltd., India) of varying capacity (2 ml, 5 ml, and 10 ml) were used for the experimental procedures. Radioactivity measurements for ^{153}Sm and ^{177}Lu were made by placing the syringe as shown in Figure 1b. A measurement made in the stock glass vial was used as a reference for geometry. The actual radioactivity contained in the syringe was difference of activity in the vial before and after filling the syringe. This difference was used for determining the accuracy of the dose calibrators for the observed syringe radioactivity measurements at different volumes. Two methods were used for documentation of the geometric variations in the radioactivity measurements (i) Constant activity and (ii) Volumetric method at a constant specific activity. In the first method, we added gravimetrically determined increasing quantity of inactive solution to a certain volume of radioactive solution already in the syringe and recorded the readings at each volume increment.

Table 1: Characteristics of radionuclides

Property	Sm-153	Lu-177
Atomic number	62	71
Gamma energy (KeV) (%)	103 (28)	113 (2.8) 208 (11)
Beta energy max (KeV)	810	497
Half-life (days)	1.93	6.74
Production mode	Sm-152 (*n, γ*)	Lu-176 (*n, γ*)
Decay mode	Beta, *γ*	Beta, *γ*
Daughter	Eu-153	Hf-177
Gamma constant (mSv/h/MBq @ 1 m)	2.44×10^{-5}	7.636×10^{-6}
HVT# (mm) for lead	0.1	0.6
TVT* (mm) for lead	0.33	2.1
Range in tissue (mm)	3.4	2.1

#HVT: Half value thickness, *TVT: Tenth value thickness

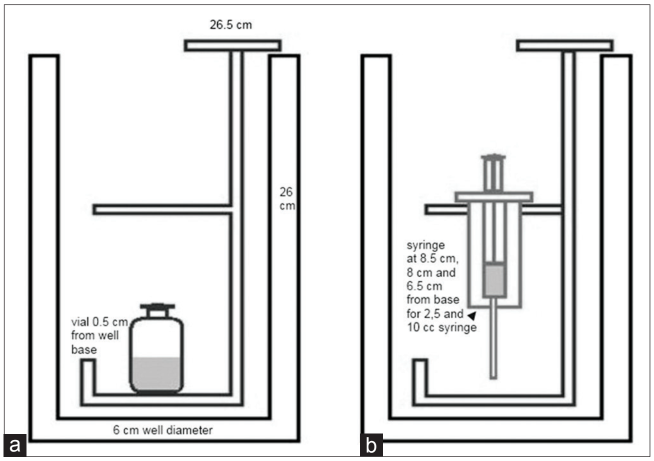

Figure 1: Block diagram of the dose calibrator with the source holder for (a) vial geometry and (b) syringe geometry

The volume was determined based on weight of the solution added to the syringe. The second method used addition of volumetrically determined quantity of radioactive solution withdrawn from the stock solution in a syringe. Syringes were assayed at each successive aliquot withdrawn from same stock solution and volume was determined by the graduation markings on the plastic syringe barrel. This generally is a method used at our institute for preparing radioactive doses for patient injections. Air was drawn up in the needle to avoid the presence of radioactive solutions in the needle itself and needle was capped before measuring the syringe in order to ensure good counting geometry. All the experiments were performed in triplicates. For each measurement, the reference volume constituted only 40.0% of the total syringe capacity, and the calibration factor was calculated using the following formula:

$$\text{Syringe volume correction} = \frac{\text{Reference volume reading}}{\text{Observed volume reading}} \qquad (2)$$

The calibration curves were obtained by fitting experimentally determined syringe volume correction factor values against the volume in the syringe/s. The student's *t*-test was applied to compare the difference in the mean activity values measured in the vial and the syringes.[15]

RESULTS

For both the dose calibrators, daily radioactivity readings of cesium-137 (constancy test) were recorded and decay corrected and were found to be in good agreement (within ± 1.0%) with the certified radioactivity values of the standard source used in the present study.

Calibration/dial setting of dose calibrators for ^{153}Sm

To start with the calibration process, ^{153}Sm radioactivity measurements were made on each of the dose calibrator using the calibration factors of technetium-99 m (80), iodine-131 (151) and thallium-201 (205). The observed readings at these settings were significantly different from the calibrated activity of the radionuclide. These channel numbers and their response factors when used in equation-1 provided a value of 230 as the dial setting factor for ^{153}Sm measurements on both the dose calibrators. As a part of the calibration procedure, BRIT, BARC certified amount of ^{153}Sm-EDTMP solution was measured in a glass vial on each dose calibrator using different dial settings/calibration factors ranging from 80 to 250. A minimum percent difference in the measured and certified radioactivity of ^{153}Sm was observed with the dial settings of 229 and 232 on both the dose calibrators [Figure 2]. At a dial setting of 230, the difference in the measured and the certified activity was negligible (<0.55%). This dial setting factor was used for all further radioactivity measurements of ^{153}Sm on both the dose calibrators. A linearity check (at dial setting of 230, for four and half half-lives [210 h]) performed on each dose calibrator over an activity range 4 MBq to 2.1 GBq of ^{153}Sm showed maximum difference of ± 5% as shown in Figure 3a.

Calibration/dial setting of dose calibrators for ^{177}Lu

The manufacturer's specified calibration/dial setting of each of the dose calibrator for ^{177}Lu was 450 × 10.[13] The radioactivity measurements of ^{177}Lu-EDTMP solution made at this dial setting underestimated the radioactivity by a factor of <9% when compared with the certified value on each of the dose calibrators. In order to derive the correct dial setting for ^{177}Lu measurements for both dose calibrators, an iterative approach was used. These measurements were made over dial settings from 80 to 710 × 10 and percentage deviations are shown in Figure 4. It was observed that calibration setting of 403 × 10 and 408 × 10 for CRC-15R and CRC-ultra dose calibrator provided the highest accuracy (~99.9%) for radioactive measurements of ^{177}Lu. The estimated factors were used for all the further measurements of ^{177}Lu on each dose calibrator. A deviation of ± 5.0% was observed when radioactivity of ^{177}Lu was measured over 4.5 half-lives of the radionuclide. Figure 3b shows the linearity curve of the CRC-15R for ^{177}Lu.

Evaluation of effect of geometric variations on radioactivity measurements

The radioactivity of ^{153}Sm and ^{177}Lu was measured in syringes of three different sizes/volumes (2 ml, 5 ml, and 10 ml) and compared with the corresponding vial readings. A statistically insignificant ($P > 0.001$) difference was observed for ^{153}Sm and ^{177}Lu for 2 ml syringe geometry. In 5 ml syringe and 10 ml geometry, a statistically significant difference ($P < 0.001$) was observed for both ^{153}Sm and ^{177}Lu. The mean activity measured in the syringe was always higher than the mean activity measured in the reference glass vial.

The results of the two different methods used for calculation of volume correction factors of syringes of varying capacity (2, 5 and 10 ml) for different radionuclides indicated that gravimetric method provided the most accurate correction factors. Figure 5 shows the syringe volume correction factor for different syringes with incremental fill volumes. The correction factors are almost constant for particular

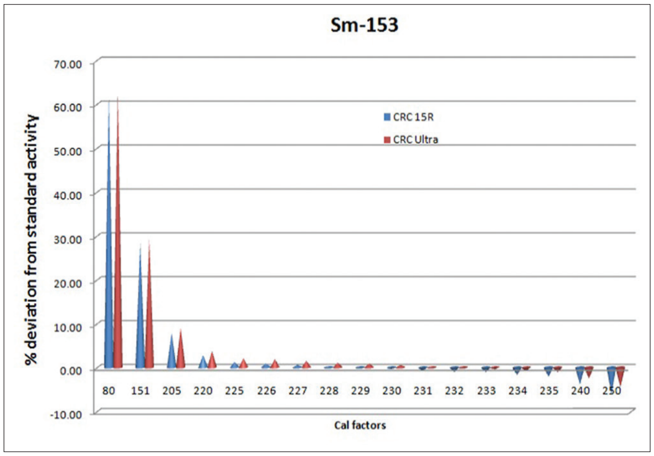

Figure 2: The percentage deviations between the measured and calibrated activity of Sm-153 on different calibration factors for both CRC-15R and CRC-ultra dose calibrators

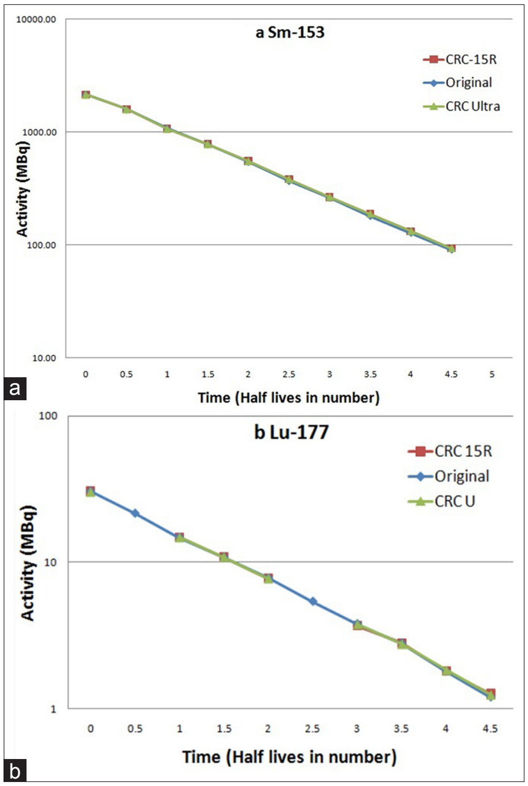

Figure 3: The linearity curve of ^{153}Sm (a) at dial setting = 230 and ^{177}Lu (b) at dial setting = 403 × 10 on both the dose calibrators. The overlay of curves shown minimal deviation from the calculated decay line

syringe geometry. However, the correction factor increased with increase in syringe capacity, but the variation ranged within ±5% only.

DISCUSSION

^{153}Sm and ^{177}Lu supplied indigenously (BRIT, BARC, Mumbai, India) as EDTMP formulations are administered to advanced stage cancer patients with widespread bone metastases. The best clinical outcome or bone pain relief is achieved when the administered dose of each of these two emitters is titrated against the patients weight (MBq/kg. body weight) as compared to the fixed dose protocols.[1] These radionuclides are supplied in standard glass vials while dose measurements by the end users are made in plastic syringes before final administration to the patients. The measurements of these radionuclides (having both beta/gamma emissions) may give rise to differences in readings when measured in a syringe or a vial. We, therefore, need to measure or account for the error (s) in measurements due to the geometry. The dose calibrators used in the conventional nuclear medicine departments are best calibrated for gamma emitters. Calibration factors of dose calibrators are either not provided for beta emitters or are inadequate and do not yield accurate measurements for these radionuclides. The National Institute of Standards and Technology, Gaithersburg, USA tabulated the results of several dial setting determinations as recommended by the instruments' manufacturers and reported that the activity readings when using these dial settings are in error of up to 50%.[3,4]

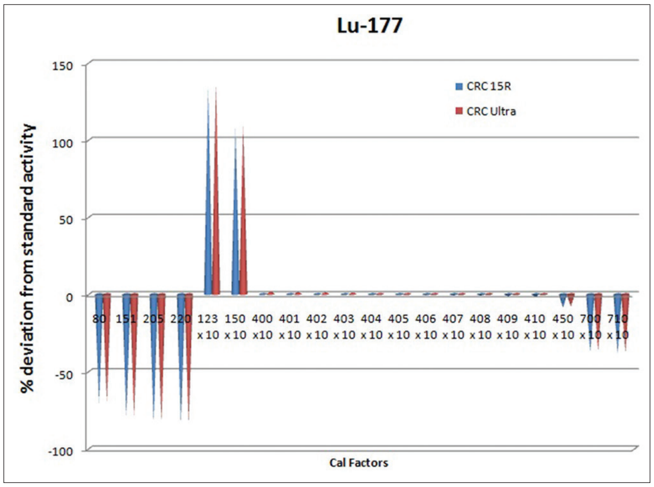

Figure 4: The percentage deviation between measured and calibrated activity of Lu-177 for different calibration settings for both CRC-15R and CRC-ultra dose calibrators

The radioactivity measurements for ^{153}Sm at an estimated dial setting of 230 for each of the two calibrators used in the present study yielded results that were in good agreement (within ± 1%) with the certified results. Further, a linearity check at dial setting of 230 for each dose calibrator over an activity range of 4 MBq to 2.1 GBq of ^{153}Sm showed a deviation of ±5%. These findings indicated that the dial setting of 230 can be used with confidence over a wide range of radioactivity of ^{153}Sm on each of the two models of dose calibrators used in the present study. We obtained a dial setting of 230 ± 2 for ^{153}Sm for two different dose calibrator models which were very close to the value 239 ± 4 reported by Plancha Mansanet *et al.* for the Capintec CRC-35R.[16] The minor deviation in the dial setting (s) could be attributed to a different model (CRC-35R) of dose calibrator used by these authors, but we did not find any significant difference in dial setting for ^{153}Sm on the two different models 229 for CRC-15R and 232 for CRC-ultra, used in the present study.

On the other hand, when we used dial setting provided by manufacturer for measurement of ^{177}Lu, both the dose calibrators underestimated radioactivity by 9% as compared with the certified (standard) radioactivity values. As described by Salako and Denardo,[17] the manufacturers' supplied dial settings may give a variation as high as 35%, which is generally abandoned by the users at a later stage or with experience. In an effort to calibrate dose calibrators and estimate accurate dial setting, we followed an iterative approach. This approach provided us a dial setting (403 × 10 for CRC-15R and 408 × 10 for CRC-ultra) that provided near 99.9% accuracy for ^{177}Lu measurements. A linearity deviation of ± 5% was observed when the given certified radioactivity of ^{177}Lu was measured over 4.5 half-lives of the radionuclide [Figure 3b].

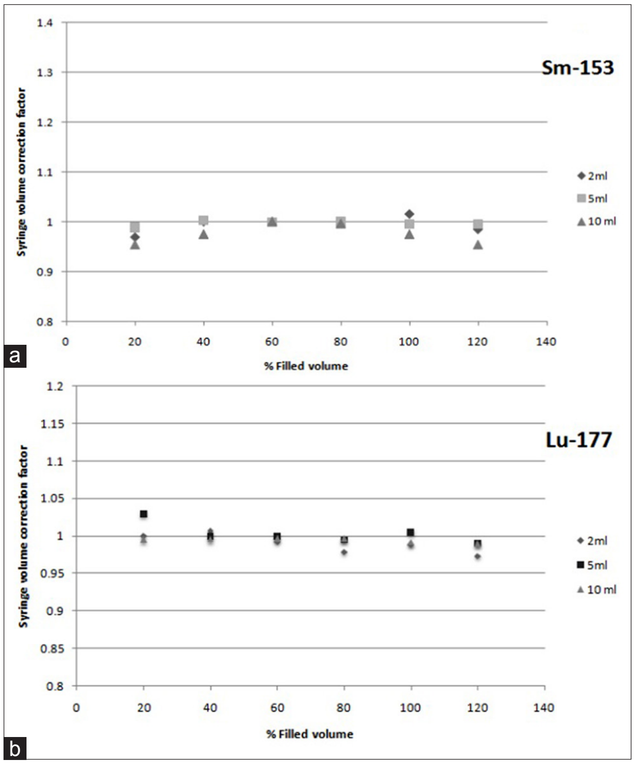

Figure 5: Syringe volume correction factors obtained for (a) ^{153}Sm and (b) ^{177}Lu for three plastic syringe geometries (2, 5 and 10 ml) in a CRC-15R dose calibrator. Similar response was observed for CRC-ultra

Measurements made in plastic syringes using both dose calibrators also overestimated the dose of each of the two radionuclides' in comparison with the measurements using a glass vial. The observed difference may be due to the positional difference of the syringe and vial in the source holders as shown in Figure 1. Generally, glass vials have multi-doses in larger volume, and it is a known fact that as the volume decreases, detection efficiency increases. Thus, plastic syringes with single patient dose in less volume overestimated the radioactivity concentration. Since, the radionuclide consignment is always provided in glass vial by the supplier, it thus becomes imperative to account for this difference due to the geometric variation (s) to have realistic dose estimates of these beta emitters prior to administration in the patients. As the syringe is used as a calibrated geometry for delivering the dose to patients, even small differences in the dose can be significant. It has been reported by Zimmerman and Cessna that even for high-energy positron emitters like fluorine-18 and copper-64, a variation of about 2.0% was observed in activity measurements made in different sample containers.[3] Zimmerman *et al.* also reported a difference of approximately 1.4% in the rhenium-188 measurements using same instrument setting but different geometries (vial and ampoule).[4] Ceccatelli *et al.* has reported a difference of 2–7% between the measured and true radioactivity for technetium-99 m and iodine-131 related to measurement geometry.[5] However, these authors reported that the magnitude of this difference was dependent on energies of emitted photons and difference was as high as 35% for indium-111 measurements. They further highlighted that the observed difference/variation could be further enhanced when measuring low energy γ ray emitters or pure β emitters. The radioactivity measurements made in plastic syringes of different capacity caused a variation of ± 5.0% in our setting that appear similar to what is already reported. To account for this variation, appropriate volume correction factors were derived experimentally in our setting [Figure 5]. This discrepancy always results in overestimation of the activity and thus low administered therapeutic dose to the patients, resulting in under-treatment or repeat treatment on the general basis. This is not a good practice, and hence we propose that users should calibrate their dose calibrators before measuring therapeutic dose for patient administration.

CONCLUSION

In order to make accurate radioactivity measurements of beta-gamma emitters, we need to redefine the manufacturers' quoted values of the dial settings of the dose calibrators used in a given hospital-based clinical setting. The error (s) in measurements due to the geometry and volumetric variations should also be considered. All these variations could lead to a cumulative error of about 20.0% toward the accuracy in the radioactivity measurements of the beta-gamma emitters. As a part of the quality assurance program, the nuclear medicine centres practicing both low/high dose beta therapies may send the standard radioactivity measurements data to the national suppliers periodically in order to the check the performance or accuracy of their dose calibrators.

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