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ORIGINAL ARTICLE

Comparison of the risk of viral infection between the living and nonliving musculoskeletal tissue donors in Australia

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Summary

Screening of musculoskeletal tissue donors with nucleic acid testing (NAT) for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) has been implemented in the United States and other developed nations. However, in contrast to the donor demographics in the United States, the majority of Australian musculoskeletal tissue donations are primarily from living surgical donors. The objective of our study was to determine and compare the risk of viral infection associated with musculoskeletal tissue donation from living and nonliving donors in Australia. We studied serum samples from 12 415 consecutive musculoskeletal tissue donors between 1993 and 2004. This included 10 937 surgical donations, and 1478 donations obtained from postmortem organ donation patients and cadaveric donors. Current mandatory retesting of surgical donors 6 months postdonation reduces the risk of viral infection by approximately 95% by eliminating almost all donors in the window period. The addition of nucleic acid amplification testing for nonliving donors would similarly reduce the window period, and consequently the residual risk by approximately 50% for hepatitis B virus, 55% for HIV, and 90% for HCV. NAT, using appropriately validated assays for nonliving donors, would reduce the residual risk to levels comparable to that in living donors (where the 95% reduction for quarantining pending the 180-day re-test is included).

Introduction

Musculoskeletal tissue is only second to the blood as the most frequently transplanted human tissue and there continues to be an enormous demand for these allografts throughout the world. Currently in Australia, the majority of musculoskeletal tissue donations are from living surgical donors, predominantly consisting of retrieved femoral heads postprimary hip arthroplasty. However, to fulfil the increasing demand for tissues, there is a trend to begin the use of materials obtained from postmortem organ donation patients and cadaveric donors.

Transplantation of tissue from a living or deceased donor exposes the recipient to viral transmission. Measures to safeguard tissue recipient's safety include a review of the donor's medical history, microbiological monitoring, bio-burden reduction, plasma haemodilution, and donor serological screening for hepatitis B surface antigen (HBsAg), and antibodies against human immunodeficiency virus (anti-HIV), hepatitis C virus (anti-HCV), and human T-cell lymphotropic virus (anti-HTLV). However, the donor-selection procedures for nonliving donors are more challenging – the medical history questionnaire has to be completed by the next-of-kin, and the

confirmatory serological testing undertaken routinely for living donors 6 months postretrieval cannot be performed in the case of nonliving donors. This article describes the prevalence and estimated incidence of HIV, hepatitis B virus (HBV), HCV, and HTLV in living donors compared with rates obtained during the same period from nonliving donors in Australia, to ascertain whether there is a greater risk of viral infection associated with tissues obtained from nonliving donors.

Methods

We studied serum samples from 12 415 consecutive musculoskeletal tissue donors from three large tissue banks in Australia between 1993 and 2004. This included 10 937 surgical donations (living donations), and 1478 donations obtained from postmortem organ donation patients and cadaveric donors (nonliving donations). Informed oral consent to tissue donation and blood sampling for virological testing was obtained from either the next-of-kin or donor who had fulfilled the medical exclusion criteria and behavioural risk assessment. Mandatory serological testing for HIV, HBV, HCV, and HTLV were performed for all specimens obtained at the time of donation, and surgical donors were required to return for a follow-up test 6 months post-tissue donation to rule out seroconversion. Allografts from these donors were not utilized until the 6-month postretrieval serology testing returned a negative result.

Determination of prevalence, estimated incidence, and estimated probability of viral infections among musculoskeletal tissue donors

Prevalence was defined as the number of donors with confirmed positive tests divided by the total number of donors tested [1]. Age- and gender-specific prevalence rates of anti-HIV, HBsAg, anti-HCV, and anti-HTLV in musculoskeletal tissue donors were obtained from databases of the Perth Bone and Tissue Bank (PBTB), Queensland Bone Bank (QBB), and Donor Tissue Bank of Victoria (DTBV) for the period 1993 through 2004. During this period, all three bone banks complied with the Code of Good Manufacturing Practice – Human Blood and Tissues [2]. First-time blood donor rates were obtained from the corresponding Australian Red Cross Blood Services (ARCBS) sites. Statistical comparisons were performed using Fisher's exact test or Pearson chi-squared test as appropriate. A P-value <0.05 indicated that a difference was significant. The 95% confidence interval (CI) for prevalence rates were obtained by the Fleiss quadratic method, which is adapted when proportions are close to zero.

The incidence rate of new infections among musculoskeletal tissue donors was estimated using a previously published method [3] as follows. First, the ratio of the reported prevalence rates in new blood donors and tissue donors was calculated. Second, it was assumed that prevalence differences between populations are proportional to incidence differences. The incidence in tissue donors was then calculated by multiplying the incidence in new blood donors by the prevalence ratio of the two populations.

The estimated risk of infectivity – the probability of an undetected window period (WP) donation occurring within the study period – was determined by the Incidence/Window Period Model [4–8]. This estimate of the residual risk of viral transmission is calculated by assessing the rate of new infection in repeat donors (viral incidence), then multiplying this by the probability of such a donor donating while being in the undetectable WP. The accuracy of this risk modelling for blood donor HIV/HCV nucleic acid testing (NAT) has been retrospectively validated, confirming its utility as a component of cost–benefit analyses [5,9–11].

Results

In total, we obtained results from 12 415 musculoskeletal tissue donors between 1993 and 2004, including 10 937 surgical donors (88.10%) and 1478 donations obtained from postmortem or cadaveric donors (11.90%). This database encompasses approximately 85% of the total number of musculoskeletal tissue donations in Australia within that period [12]. On average, there were 918 living donors (range: 380–2212) and 123 nonliving donors (range: 63–261) screened per year, and 45.58% of all donors were female.

Prevalence of viral infections among living and nonliving donors

Age- and gender-matched prevalence rates among 10 937 surgical musculoskeletal tissue donors for the period 1993–2004 are shown in Table 1. Surgical donors were mostly in the older age group as donors tend to be patients undergoing joint replacement procedures. Approximately 95% of living donors were 50 years of age or older (median age 65 years [inter-quartile range (IQR): 59–73 years)] and 49.14% were female. The prevalence rate (per 100 000 persons) amongst surgical donors was 64.00 (95% CI, 25.75–131.48) for anti-HIV, 342.34 (95% CI, 241.04–471.21) for HBsAg, 570.48 (95% CI, 437.61–730.92) for anti-HCV, and 111.82 (95% CI, 58.09–195.26) for anti-HTLV.

The prevalence rates of confirmed positive results for viral infection among deceased donors, stratified accord-

Table 1. Prevalence of viral markers among living musculoskeletal donors, according to age and gender (1993–2004).

	Male donors (prevalence per 100 000 persons)		Female donors (prevalence per 100 000 persons)		All donors (prevalence per 100 000 persons)	
	Number tested	Confirmed positive	Number tested	Confirmed positive	Number tested	Confirmed positive
Anti-HIV						
<30	35	0 (0.00)	31	0 (0.00)	66	0 (0.00)
30–49	305	0 (0.00)	218	0 (0.00)	523	0 (0.00)
≥50	5223	4 (76.58)	5125	3 (58.54)	10 348	7 (67.65)
Total	5563	4 (71.90)	5374	3 (55.82)	10 937	7 (64.00)
HBsAg						
<30	29	0 (0.00)	31	0 (0.00)	60	0 (0.00)
30–49	297	3 (1010.10)	211	0 (0.00)	508	3 (590.55)
≥50	5166	16 (309.72)	5074	18 (354.75)	10 240	34 (332.03)
Total	5492	19 (345.96)	5316	18 (338.60)	10 808	37 (342.34)
Anti-HCV						
<30	30	0 (0.00)	31	0 (0.00)	61	0 (0.00)
30–49	298	3 (1006.71)	214	3 (1401.87)	512	6 (1171.88)
≥50	5203	31 (595.81)	5092	25 (490.97)	10 295	56 (543.95)
Total	5531	34 (614.72)	5337	28 (524.64)	10 868	62 (570.48)
Anti-HTLV						
<30	31	0 (0.00)	33	0 (0.00)	64	0 (0.00)
30–49	301	0 (0.00)	210	0 (0.00)	511	0 (0.00)
≥50	5128	6 (117.01)	5029	6 (119.31)	10 157	12 (118.15)
Total	5460	6 (109.89)	5272	6 (113.81)	10 732	12 (111.82)

Table 2. Prevalence of viral markers among nonliving musculoskeletal donors, according to age and gender (1993–2004).

	Male donors (prevalence per 100 000 persons)		Female donors (prevalence per 100 000 persons)		All donors (prevalence per 100 000 persons)	
	Number tested	Confirmed positive	Number tested	Confirmed positive	Number tested	Confirmed positive
Anti-HIV						
<30	261	0 (0.00)	56	0 (0.00)	317	0 (0.00)
30–49	449	1 (222.72)	111	0 (0.00)	560	1 (178.57)
≥50	483	0 (0.00)	118	0 (0.00)	601	0 (0.00)
Total	1193	1 (83.82)	285	0 (0.00)	1478	1 (67.66)
HBsAg						
<30	261	3 (1149.43)	55	0 (0.00)	316	3 (949.37)
30–49	449	8 (1781.74)	109	0 (0.00)	558	8 (1433.69)
≥50	483	2 (414.08)	116	0 (0.00)	599	2 (333.89)
Total	1193	13 (1089.69)	280	0 (0.00)	1473	13 (882.55)
Anti-HCV						
<30	261	0 (0.00)	55	1 (1818.18)	316	1 (316.46)
30–49	449	0 (0.00)	111	1 (900.90)	560	1 (178.57)
≥50	483	2 (414.08)	118	0 (0.00)	601	2 (332.78)
Total	1193	2 (167.64)	284	2 (704.23)	1477	4 (270.82)
Anti-HTLV						
<30	154	0 (0.00)	36	0 (0.00)	190	0 (0.00)
30–49	228	1 (438.60)	75	0 (0.00)	303	1 (330.03)
≥50	244	1 (409.84)	18	0 (0.00)	262	1 (381.68)
Total	626	2 (319.49)	129	0 (0.00)	755	2 (264.90)

ing to age and gender, are shown in Table 2. In contrast to surgical donors, 21.45% of nonliving donors were less than 30 years of age, 37.89% 30–49 years of age, and 40.66% 50 years of age or older [median age 46 years (IQR: 39–53 years)]. In addition, only 19.28% of deceased donors were female. Excluding anti-HCV, the prevalence

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Table 3. Estimated incidence and probability of undetected viral infections among living and nonliving musculoskeletal tissue donors in Australia.

		Estimated incidence rate* per 100 000 person-years	Estimated probability† (antibody) per 100 000 donors (95% CI)	Estimated probability (NAT)
Living donors	Anti-HIV	12.88	0.78 (0.21–1.34)	0.32 (0.28–0.36)
	HBsAg	3.53	0.42 (0.36–0.48)	0.21
	Anti-HCV	10.71	1.94 (1.12–2.76)	0.22 (0.18–0.26)
	Anti-HTLV	5.49	0.77 (0.54–1.08)	–
Nonliving donors	Anti-HIV	13.61	0.82 (0.22–1.42)	0.34 (0.29–0.38)
	HBsAg	9.61	1.15 (0.98–1.31)	0.57
	Anti-HCV	5.08	0.92 (0.53–1.31)	0.10 (0.08–0.12)
	Anti-HTLV	13.02	1.82 (1.28–2.57)	–

*Estimated incidence in tissue donors (per 100 000 person years) = {(prevalence in tissue donors)/(prevalence in first-time blood donors)} × incidence in first-time blood donors [3,19].

Tissue donor prevalence rates were retrieved from databases of the Perth Bone and Tissue Bank, Queensland Bone Bank, and Donor Tissue Bank of Victoria. First-time blood donor prevalence rates were retrieved from databases of the corresponding Australian Red Cross Blood Services (ARCBS) sites.

Incidence in first-time blood donors (per 100 000 person-years) = (number of seroconverters × 100 000 × 2.03)/(number of repeat donors × 0.42) [4,5].

First-time blood donor incidence rates were derived by multiplying the repeat donor incidence rates by a correction factor of 2.03, and the number of person-years of observation which is equivalent to 0.42, as calculated by the standard incidence method in a published study of Australian blood donors [4,5].

Further, the incidence of HBV was multiplied by the ARCBS adjustment factor of 1.88 to compensate for the potential underestimation of HBV incidence because of the transient nature of hepatitis B surface antigen.

†Estimated probability of viremia = (window period/365 days) × incidence rate; 95% CIs were calculated from the 95% CIs of the window periods (WP).

Antibody WP: 22 (95% CI, 6–38) for anti-HIV [13], 43.6 (95% CI, 37.4–49.7) for HBsAg [14], 66 (95% CI, 38–94) for anti-HCV [7,15], 51 (95% CI, 36–72) for anti-HTLV [16].

NAT WP: 9 (95% CI, 7.8–10.2) for anti-HIV [11], 21.8 for HBsAg [14], 7.4 (95% CI, 6.1–8.7) for anti-HCV [11].

of viral infection was higher for deceased donors than surgical donors. The rate of confirmed positive results (prevalence rate per 100 000 persons) for nonliving donors was 67.66 (95% CI, 1.85–376.06) for anti-HIV, 882.55 (95% CI, 471.01–1504.53) for HBsAg, 270.82 (95% CI, 73.79–691.96) for anti-HCV, and 264.90 (95% CI, 32.34–953.91) for anti-HTLV. However these differences only reached statistical significance for HBV infection (882.55 vs. 342.34, $\chi 2 = 9.29$, $P = 0.002$).

Estimated incidence and estimated risk of infectivity among living and nonliving donors

Table 3 compares the estimated incidence rates and the predicted NAT yield for HIV, HBV, HCV, and HTLV between living and nonliving donors. We determined the incidence rates among tissue donors by extrapolating from the rates among first-time blood donors. The incidence of HBV was adjusted by a correction factor to compensate for potential underestimation because of the transient nature of HBsAg [4,5]. We estimated the incidence rates among surgical donors were 12.88 per 100 000 person-years for HIV, 3.53 per 100 000 person-years for HBV, 10.71 per 100 000 person-years for HCV, and 5.49 per 100 000 person-years for HTLV. Besides anti-HCV, the estimates derived for nonliving donors were higher than those derived for living donors, though none of these differences reached statistical significance. The incidence rates for nonliving donors were estimated to be 13.61, 9.61, 5.08, and 13.02 per 100 000 person-years respectively.

The estimated probability that a living donor was viraemic at the time of donation was 1 in 128 000 for HIV, 1 in 238 000 for HBV, 1 in 52 000 for HCV, and 1 in 130 000 for HTLV. With the addition of NAT, this would be reduced to 1 in 312 000 for HIV, 1 in 476 000 for HBV, and 1 in 455 000 for HCV. Similarly, if individual NAT testing were to be used for nonliving tissue donors, the probability of donor viraemia would be reduced to 1 in 294 000 for HIV, 1 in 174 000 for HBV, and 1 in 1 000 000 for HCV.

Discussion

Given its increasing popularity, it is important for medical professionals and the general population to be aware of the risks of transfusion-transmitted diseases associated with musculoskeletal tissue transplantation and the limits of the screening tests used. By way of testimony to the relative safety of the existing Australian system, not a

single case of viral infection on account of musculoskeletal tissue transplantation is known to have occurred in Australia since 1993. This finding is consistent with the residual risk estimates derived here, given the number of donors screened to date (12 415) and the highest estimate (HCV in living donors) of 1 in 52 000 would not as yet predict the occurrence of a breakthrough infection.

With the exception of HCV, prevalence rates of viral infection were higher among deceased donors than surgical donors. Estimated incidence rates were also higher among nonliving donors, with the difference between the incidence rates for HBV and HTLV close to reaching statistical significance (3.53 vs. 9.61 for HBsAg, $\chi 2 = 3.27$, $P = 0.071$; and 5.49 vs. 13.02 for anti-HTLV, $\chi 2 = 3.56$, $P = 0.059$). The underlying causes of these differences could be related to the changes in the risks of these pathogens in the general population, changes in factors that occur around the time of donation, and by the risk factors that are present in early life (age-period-cohort effect). For example young adults in the 1960s and 1970s may have experimented with intravenous drugs and become infected with HCV, and these people would have entered into the 50 years and older age-group during the late 1990s and early 2000. Similar findings were observed in a recent study by Zou *et al.* [17], which showed significant downward trend in the prevalence of all major blood-borne infections among first-time blood donors in the United States with the exception of anti-HCV amongst male 50–59 years of age.

In the context of the recipient risk, it is important to note that the risk estimates we derive for living donor allografts are conservative because they do not consider the risk reduction contributed by the requirement to re-test the donor 6 months after donation. Although it is difficult to accurately determine the quantitative impact of this intervention perhaps it is best considered in the context of the estimated WP for each virus. The upper 95% CI for the duration of the WP is 38 days for anti-HIV, 94 days for anti-HCV, 49.7 days for HBsAg and 72 days for anti-HTLV [7,13–16]. Assuming the worst case scenario where infection occurred on the day of retrieval and the donor was re-tested 180 days postsurgery, then the probability that the donor's infection remains undetectable on both occasions is reduced by more than 95% for all viral markers, as the upper 95% CI for the WP is <180 days.

Despite the low residual risk of viral infection, it is imperative that new interventions with the potential to further reduce the risk are carefully considered as they become available. NAT for HIV and HCV RNA is an example, which has already been widely implemented for screening blood donors as well as for tissue allografts in the United States, where the majority are sourced from nonliving donors [19]. NAT reduces the WP (and consequently the residual risk) by 55% for HIV (WP reduced from 22 to 9 days) and approaching 90% for HCV (WP reduced from 66 to 7.4 days) [11,14]. More recently some countries have also implemented NAT for HBV DNA, which when performed on single blood donations can reduce the WP by approximately 50%. For living donors where retesting already eliminates the majority of the WP infections, NAT may only be clinically significant to prevent HCV transmission from a seronegative HCV RNA-positive donor. A recent French study of NAT in tissue donors showed that serosilent infection may have contributed to 0.2% of confirmed positive HCV infections [18]. In the context of nonliving donors, NAT is certainly a more attractive option given its ability to markedly reduce the WP and consequently the residual risk.

Another benefit in favour of the use of NAT instead of the 180-day retesting for living donors would be the opportunity of increasing the supply of tissue available on account of the inclusion of some donations which would have been deferred from the failure of surgical patients to return for serological retesting. Currently the rate of patients who fail to return for retesting and have completed all other medical exclusion criteria is 10–12% approximately [12]. In a setting where surgical bone is the most significant component of the tissue banking program, and the annual demand appears to be growing faster than the Australian supply, this last reserve may be considered as a viable potential tissue source.

Evidence from countries which have implemented NAT has shown it to be cost-ineffective. However, NAT for HIV and HCV is now mandatory for both tissue and blood products in most developed nations. The results from this study show that the risk of viral infection among living and nonliving musculoskeletal tissue donors in Australia is low, though the differential risk profile between the two donor groups is problematic. One potential solution to address the imbalance is consideration of NAT using appropriately validated assays for nonliving donors which would reduce the residual risk to levels comparable to that in living donors (where the 95% reduction for quarantining pending the 180-day re-test is included).

Authorship

FY: designed and performed study, wrote paper. CS: performed study, contributed to study data and writing of paper. AF: contributed to design of study. DM: contributed to design of study and data. DW: designed study. M-HZ: designed study, contributed to study data and writing of paper.

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