THE VALUE OF QUANTITATIVE BONE SCINTIGRAPHY IN THE PROGNOSIS OF FRACTURE HEALING

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SUMMARY – Studies of fracture healing are aimed at differentiating normal from delayed bone union. Delayed union, nonunion with the development of pseudarthrosis, and infection are complications of fracture healing. In the present study, quantitative analysis by three-phase bone scintigraphy was evaluated in the early prognosis of the course of fracture healing, to assess its potential in the early detection and therapy of healing complications. In 105 patients with long bone fractures, three-phase bone scintigraphy was performed early (day 4-7), and 3 weeks, 3 months and 6 months of injury. Based on clinical, laboratory and radiological findings, patients were retrospectively divided into four groups of normal healing, pseudarthrosis, delayed union, and healing with infection. The region of interest method was used to analyze all three scintigraphy phases, i.e. perfusion, vascular space image, and static scintigram at 3 h of injection. Comparison of impulse count in the fracture area with the contralateral, intact side produced a relative index for each step of three-phase scintigraphy. Infection at the fracture site can be suspected on the basis of perfusion index in the earliest stages following injury. Delayed bone union can also be predicted very early, within three weeks of injury, by use of perfusion index. Quantitative analysis of the vascular space phase and late static scintigrams can contribute to the diagnosis of complications, however, only in later stages of disease, which in part limits their clinical relevance. Three-phase bone scintigraphy is a valuable study when expecting problems in the process of bone union.

Key words: *Fractures – healing; Bone and bones – diagnosis; Bone and bones – radionuclide imaging; Fractures – radionuclide imaging*

Introduction

Delayed bone union, pseudarthrosis (nonunion) and infection are complications of fracture healing. Studies of fracture healing are aimed at the earliest possible detection of complications, which may occasionally be difficult to diagnose by clinical examination and conventional radiography, especially at an early stage. Therefore, efforts have been invested to find new diagnostic procedures to obtain this information at an early stage of disease. One of these methods is bone scintigraphy.

Since the introduction of bone scintigraphy as a diagnostic method, attempts have been made to assess metabolic activity of the fractured bone, to predict fracture outcome and rate of bone union according to the method of treatment, and to diagnose the possible complications of healing as early as possible by quantitative analysis of radiopharmaceutical accumulation in the fracture area. Mondal *et al.* determined metabolic activity in the fracture area by quantitative analysis of delayed static scintigrams comparing the activity ratio on scintigrams obtained at 4 and 24 h of radiopharmaceutical injection, whereas Etchebehere *et al.* demonstrated activation of distal growth regions of fractured femurs in children, comparing their activity with the activity in the contralateral growth region[1,2]. On predicting union of differently treated tibial fractures, Wallace *et al.* compared scintigram activity of vascular spaces at the fracture site with the activity of contralateral, healthy site, and recorded different indexes characteristic of a par-

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ticular mode of treatment[3]. The inability to identify healing complications by quantitative analysis of delayed static scintigrams has been reported by a number of authors[4-7]. Jacobs *et al.* performed quantitative analysis in the first 15 minutes of a dynamic study divided into two parts, i.e. analysis of the vascular space phase, allowing them to differentiate patients with normal bone union, delayed bone union, and pseudarthrosis. They compared radiopharmaceutical accumulation in the fracture area with that in the healthy segment of the same bone, with monthly follow up. The monthly gain in the radiopharmaceutical accumulation ratio was 3% in patients with normal bone union, 1.4% in patients with delayed bone union, and 0% in patients with pseudarthrosis[8]. Delayed bone union and pseudarthrosis may occasionally be very difficult or even impossible to differentiate. Matin proposes comparison of quantitative data with data from a data bank of patients with healing complications[9]. Others report on the use of data between 5 and 15 minutes of radiopharmaceutical injection for quantitative analysis, i.e. the vascular space phase, with a healthy region of the same bone used for comparison. This method showed a 90% sensitivity in the detection of fractures with normal union and 70% sensitivity in the detection of healing complications[10,11].

In the light of considerable controversies about the possibilities offered by bone scintigraphy in predicting complications of fracture healing, we embarked upon this study to assess the value of particular steps of three-phase bone scintigraphy in patients with long bone fractures, associated with the highest rate of healing complications.

Patients and Methods

The study included 105 patients with open, surgically treated fractures of the femur, tibia and fibula. Patients were retrospectively divided into four groups according to clinical, laboratory and radiological findings, as follows: group 1 (n=31), mean age 32.1 (range 19-60), with normal fracture healing; group 2 (n=22), mean age 24.8 (range 18-39), with pseudarthrosis; group 3 (n=28), mean age 33.4 (range 20-55), with delayed bone union; and group 4 (n=24), mean age 38.2 (range 28-61), with infection.

Following i.v. administration of 555-740 MBq Medrotec Tc-99m-methylene diphosphonate (MDP), manufactured by Sorin-Biomedica, three-phase bone scintigraphy was performed by a Siemens large field gamma camera with a low-energy high-resolution collimator, connected to a PDP-11 computer. One-second sequences were taken during the first minute of the radiopharmaceutical administration. Early delayed scintigram showing an image of radiopharmaceutical distribution in the vascular space, thus called blood pool scintigram, was acquired 15 minutes of injection. Delayed static scintigrams were acquired three hours of injection. Total number of impulses *per* projection for vascular space and delayed static scintigram was 500,000 impulses.

Quantitative analysis by the region of interest (ROI) method was performed in each of the three phases of dynamic bone scintigraphy. The number of impulses in fracture ROI was compared with the number of impulses in a symmetric ROI of the contralateral intact bone. Thus, the relative index (RI) denoting the activity ratio between the pathologically altered bone and normal bone[12-15] was determined for each of the three-phase bone scintigraphy phases, i.e. perfusion, vascular space and late static scintigram.

Bone scintigraphy was performed early upon injury (day 4-7), then at 3 weeks, and 3 and 6 months of injury. This procedure produced a diagram of the RI pattern in each individual patient and each phase of three-phase bone scintigraphy. No additional surgical interventions were performed during the study period. The group of 24 patients that developed infection received antibiotics for the first 3 months postoperatively, and eight (33.3%) of these patients for another 3 months, i.e. to the end of scintigraphic monitoring.

On statistical analysis, Kruskal-Wallis analysis of variance and Mann-Whitney test were employed.

Results

Results are presented in Tables 1-3 and Figure 1. The highest mean values of perfusion RI were recorded in the group with infection, with a statistically significant difference from other patient groups. Perfusion RI was significantly higher in the group with delayed bone union than in those with normal bone union and pseudarthrosis, yet being significantly lower in comparison with infection. There was no perfusion difference between the groups with normal bone union and pseudarthrosis, where it only slightly exceeded perfusion recorded in the contralateral, healthy bone.

Figure 1 shows the highest perfusion RI to be recorded in the group of patients with infection early after injury, to decline over the next 6 months while still being twofold RI found in normal bone union. In the

Table 1. Bone perfusion mean relative index (RI) in patients with normal bone union, pseudarthrosis, delayed bone union, and infection during the study period

Perfusion relative index										
	1	2	3	4	*(p<0.05);			NS (p>0.05)		
Time after injury	Normal bone union	Pseud-arthrosis	Delayed bone union	Infection	1:2	1:3	1:4	2:3	2:4	3:4
Early	1.05±0.07	1.17±0.04	1.66±0.38	3.36±0.64	NS	*	*	*	*	*
3 weeks	1.14±0.12	1.11±0.04	1.91±0.36	3.11±0.66	NS	*	*	*	*	*
3 months	1.08±0.06	1.11±0.04	1.79±0.31	2.43±0.65	NS	*	*	*	*	*
6 months	1.05±0.05	1.09±0.02	1.50±0.36	2.11±0.63	NS	*	*	*	*	*

NS = non-significant

Table 2. Bone vascular space mean relative index (RI) in patients with normal bone union, pseudarthrosis, delayed bone union, and infection during the study period

Vascular space relative index										
	1	2	3	4	*(p<0.05);			NS (p>0.05)		
Time after injury	Normal bone union	Pseud-arthrosis	Delayed bone union	Infection	1:2	1:3	1:4	2:3	2:4	3:4
Early	3.53±0.68	3.05±0.15	3.32±0.94	3.01±0.90	NS	NS	NS	NS	NS	NS
3 weeks	3.11±0.71	3.12±0.16	3.53±0.90	3.22±0.73	NS	NS	NS	NS	NS	NS
3 months	2.88±0.68	3.11±0.14	3.44±0.83	2.79±0.82	NS	*	NS	*	NS	*
6 months	2.74±0.68	3.13±0.10	3.28±0.72	2.36±0.47	NS	*	NS	*	*	*

NS = non-significant

Table 3. Bone static scintigram mean relative index (RI) in patients with normal bone union, pseudarthrosis, delayed bone union, and infection during the study period

Static scintigram relative index										
	1	2	3	4	*(p<0.05);			NS (p>0.05)		
Time after injury	Normal bone union	Pseud-arthrosis	Delayed bone union	Infection	1:2	1:3	1:4	2:3	2:4	3:4
Early	4.38±1.07	4.06±0.58	4.00±1.06	4.26±1.24	NS	NS	NS	NS	NS	NS
3 weeks	3.92±1.01	3.76±0.42	4.14±0.99	4.45±1.17	NS	NS	NS	NS	NS	NS
3 months	3.65±0.97	3.79±0.37	4.06±0.88	3.94±1.33	NS	NS	NS	NS	NS	NS
6 months	3.54±0.95	3.83±0.44	3.81±0.87	3.36±0.66	NS	NS	NS	NS	*	*

NS = non-significant

group with delayed bone union, perfusion RI showed highest value at 3 weeks of injury, which slowly declined thereafter to the values that still were statistically significantly higher than those recorded in the groups with normal bone union and pseudarthrosis.

Vascular space RI showed no significant between-group differences early after and 3 weeks of injury. At 3 and 6 months of injury, RI showed highest value in the group of patients with delayed bone union. At 3 and 6 months of injury, vascular space RI recorded in the group

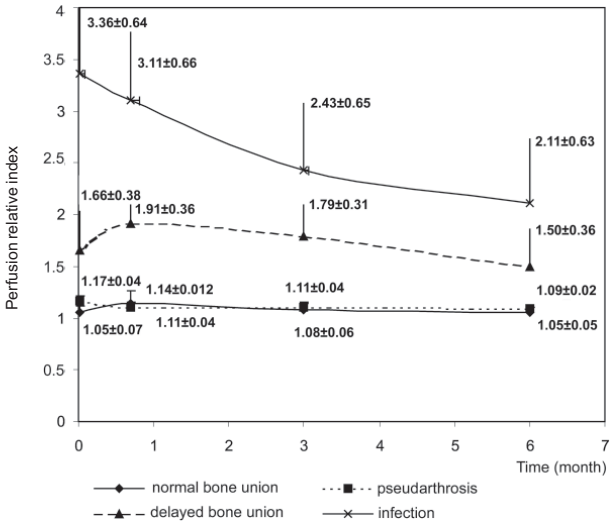

Fig. 1. Graphic presentation of bone perfusion mean relative index (RI) in patients with normal bone union, pseudarthrosis, delayed bone union, and infection during the study period.

of patients with delayed bone union differed significantly from those observed in other patient groups. In this group, the highest vascular space RI persisted through the end of the study period.

Delayed static RI recorded in the group of patients with infection showed a statistically significant difference from the values found in the groups with delayed bone union and pseudarthrosis, however, only at 3 months of injury.

Discussion

Studies reported to date have shown that dynamic scintigraphy of the fracture area has a prognostic value in the diagnosis of fracture healing complications, with a major role attributed to quantitative analysis of the vascular space phase[8,10,11]. In our study, quantitative analysis of perfusion phase yielded most valuable results. The highest relative index of perfusion was recorded in patients with infection early upon injury. Such a result could be anticipated because perfusion, along with the bone metabolic activity, is one of the major factors determining the intensity of radiopharmaceutical accumulation that is significantly enhanced by inflammation.

In patients with infection, the values of perfusion index early upon trauma were threefold those recorded in patients with normal bone union and pseudarthrosis, to decrease with time when inflammation regression reduced the fracture area perfusion.

Perfusion RI was higher in patients with delayed bone union than in those with normal fracture healing and bone nonunion, being highest at 3 weeks of injury. Thus, it proved useful in differentiating delayed bone union and bone nonunion very early after injury. Perfusion RI is most valuable for its ability to identify patients suspected for infection early upon injury and patients in whom delayed bone union is likely to occur, which is confirmed by the perfusion index dynamics. Perfusion RI cannot differentiate patients with normal healing and those with bone nonunion.

Vascular space RI was significantly higher in patients with delayed bone union in comparison with other study groups at 3 and 6 months of injury, and these high values persisted to the end of the study period. Such a pattern could be explained by the continuous metabolic activity at the site of bone fracture, i.e. by the prolonged metabolic activity of fracture fragments.

Delayed static scintigram activity RI was significantly higher in patients with pseudarthrosis and delayed bone union than in those with infection at 6 months of injury. In the former two patient groups, these high RI values persisted throughout the 6-month period as the result of retarded metabolic process in the bone.

Conclusion

Results of the present study showed the three-phase bone scintigraphy to be a highly reliable tool in the diagnosis of fracture healing complications. An infection at the fracture site can be suspected from the perfusion index pattern in the early stage following injury. Delayed bone union can also be predicted by use of perfusion index and reliably differentiated from pseudarthrosis very early, i.e. within 3 weeks of injury. Quantitative analysis of the vascular space phase and delayed static scintigrams can contribute to the diagnosis of healing complications, however, in later stages of disease.

References

1. MONDAL A, BHATNAGER A, SHARMA R, BEHARI V, SAWROOP K, KHANNA CM. Evaluation of the healing process in fractures using early and delayed bone scanning. Australas Radiol 1994;38: 284-7.
2. ETCHEBEHERE EC, CARON M, PEREIRA JA, LIMA MC, SANTOS AO, RAMOS CD, BARROS FB, SANCHES A, SANTOS-JESUS R, BELANGERO W, CAMARGO EE. Activation of the growth plates on three-phase bone scintigraphy: the explanation for the overgrowth of fracture femurs. Eur J Nucl Med 2001;28:72-80.

3. WALLACE AL, STRACHAN RK, BLANE A, BEST JJ, HUGHES SP. Quantitative early phase scintigraphy in the prediction of healing of tibial fractures. Skeletal Radiol 1992; 21:241-5.
4. GREGG PJ, BARSOUM MK, CLAYTON CB. Scintigraphic appearance of the tibia in the early stages following fracture. Clin Orthop 1983;175:139-46.
5. GUMERMAN LW, FOGEL SR, GOODMAN MA, HENLEY EN, KAPPAKAS GA, RUTKOWSKI R, LEVINE G. Experimental fracture healing: evaluation using radionuclide bone imaging. J Nucl Med 1978;19:1320.
6. JOHANNSON A. Fracture healing controlled by 87m Sr uptake. Acta Ortop Scand 1973;44:628.
7. O'REILLY RJ, COOK DJ, GAFFNEY RD, ANGEL KR, PETERSON DC. Can serial scintigraphic studies detect delayed fracture union in man? Clin Orthop 1981;160: 227-32.
8. JACOBS RR, JACKSON RP, PRESTON DF. Dynamic bone scanning in fractures. Injury 1981;12:455-9.
9. MATIN P. The bone scan in traumatic and sports injuries. In: FOGELMAN I, ed. Bone scanning in clinical practice. London: Springer-Verlag, 1986;121-32.
10. RYAN PJ, FOGELMAN I. The role of nuclear medicine in orthopedics. Nucl Med Commun 1994;15:341-60.
11. SMITH MA, JONES EA, STRACHAN RK. Prediction of fracture healing in the tibia by quantitative radionuclide imaging. J Bone Joint Surg 1987;69:441-7.
12. CRANAGE RW. A film densitometer method of bone scan quantification. Br J Radiol 1984;57:831-2.
13. PFEIFER JP, BULL U, PFEIFER H. Quantitative assessment of ^{99m}Tc-MDP scans in the investigation of diffuse alterations in bone. Eur J Nucl Med 1979;4:407-12.
14. PITT WR, SHAARP PF. Comparison of quantitative and visual detection of new focal bone lesions. J Nucl Med 1985;26:230-6.
15. VELLENGA CJLR, PAUWELS EKJ, BIJVOET OLM. Comparison between visual assessment and quantitative measurement of radioactivity on the bone scintigram in Paget's disease of bone. Eur J Nucl Med 1984;9:533-7.

Sažetak

ZNAČENJE KVANTITATIVNOG SCINTIGRAMA KOSTI U PROGNOSTICI ZARAŠTANJA PRIJELOMA

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Ispitivanje zaraštanja prijeloma ima za cilj razlikovanje normalnog od usporenog zaraštanja kosti. Odloženo zaraštanje, nezaraštanje s razvojem pseudoartroze te infekcija komplikacije su zaraštanja prijeloma. S ciljem što ranijeg otkrivanja, a time i ranije terapije komplikacija, željeli smo ispitati mogućnosti kvantitativne analize troetapne scintigrafije kosti u ranoj prognozi tijeka zaraštanja prijeloma. U 105 ispitanika s prijelomima dugih kostiju učinjena je troetapna scintigrafija kosti neposredno nakon traume (4.-7. dan nakon traume), te 3 tjedna, 3 i 6 mjeseci nakon traume. Ispitanici su na osnovi kliničkih, laboratorijskih i radioloških nalaza retrospektivno podijeljeni u četiri skupine: normalno zaraštanje, pseudoartroza, odloženo zaraštanje i zaraštanje uz infekciju. Metodom regije interesa (ROI) analizirali smo sve tri faze scintigrama: perfuziju, snimku vaskularnih prostora, te statički scintigram 3 sata nakon injiciranja. Uspoređujući broj impulsa područja frakture s kontralateralnom, zdravom stranom dobili smo relativne indekse (RI) za svaku fazu troetapne scintigrafije. U najranijim stadijima nakon povrede moguće je, na temelju indeksa perfuzije, posumnjati na infekciju na mjestu frakture. Odloženo zaraštanje također se može predskazati indeksom perfuzije vrlo rano, unutar tri tjedna od prijeloma. Kvantitativna analiza faze vaskularih prostora i kasnih statičkih scintigrama može doprinijeti dijagnostici komplikacija, ali u kasnim fazama bolesti, što donekle umanjuje njihovo kliničko značenje. Troetapna scintigrafija kosti vrijedna je pretraga u slučajevima kada se očekuju problemi zaraštanja kosti.

Ključne riječi: *Prijelomi – zaraštanje; Kost i kosti – dijagnostika; Kost i kosti – radionuklidni prikaz; Prijelomi – radionuklidni prikaz*