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We would welcome the authors’ comments on this point.

The use of graduated compression stockings in association with fondaparinux in surgery of the hip: a multicentre, multinational, randomised, open-label, parallel-group comparative study

Sir,

We read with interest the paper by Cohen et al1 in the July 2007 issue entitled, ‘The use of graduated compression stockings in association with fondaparinux in surgery of the hip: a multicentre, multinational, randomised, open-label, parallel-group comparative study’. The study showed no difference in venous thromboembolism rates between the group that was administered fondaparinux alone, and that given fondaparinux and graduated compression stockings. The authors therefore suggested the use of graduated compression stockings following hip surgery be reconsidered when fondaparinux thromboprophylaxis is used.

The methodology included an initial calculation of required sample size. Various factors were considered, including an assumed event rate (rate of venous thromboembolism) for fondaparinux alone and with stockings, and allowing for 10% of patients missing the endpoint, an 80% power and a 5% significance level required a sample size of 1072 patients (536 per group) was postulated.

We noticed, however, that “the study was stopped early because the differences between the groups were so small that it would have been futile to continue”. After various exclusions, 856 patients were included in the study, some 200 patients short of the target study size.

We question the decision to stop the study early and suggest this is a serious limitation to the methodology. If one treatment group had vastly superior results to the other, there would be ethical grounds to stop the study early. However, when there is no early difference between the groups, the study must be continued until the required sample size is attained so that the study has sufficient power. Otherwise there is the risk of a type II error - that a significant difference between the two treatments is not detected when in reality there is one.

We would welcome the authors’ comments on this point.

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Author’s reply:

Sir,

We thank Mr Boutros and his colleagues for their interest in our paper and for raising this issue. There are three main common reasons for stopping a study. They are safety, the findings of overwhelming superiority and the findings of a lack of difference, resulting in futility.

Mr Boutros and his colleagues are correct that a type II error may occur if there are lesser differences or a lower frequency of events found than hypothesised. In that case, it would be reasonable not only to continue the study to completion, but also to consider increasing the sample size to find a smaller, but clinically (and statistically) significant difference. However, in our study the results were so similar that the chances of finding a difference were minute, and more importantly, the differences seen were clinically insignificant. An estimated sample size of over 31,000 would have been required to demonstrate such a clinically significant difference. Therefore, stopping the trial for reasons of futility was appropriate.

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Surgical site infection with methicillin-resistant Staphylococcus aureus after primary total hip replacement

Sir,

We read with great interest the paper by Walls et al1 in the March 2008 issue entitled ‘Surgical site infection with methicillin-resistant Staphylococcus aureus after primary total hip replacement’, in which the authors have highlighted the efforts involved in treatment of MRSA prosthetic joint infections and formulated a treatment protocol.

A prosthetic joint infection is a major source of morbidity and patients are subjected to prolonged antibiotic therapy. Antibiotic pressure is known to select mutants that can survive the adverse treatment protocol. There is no doubt that the complexity in treating MRSA has been exacerbated through the emergence of community-acquired infections as well as vancomycin-resistant strains. Consequently, there needs to be continuing development of agents effective against this multi-drug-resistant organism with newer antibiotics such as daptomycin, tigecycline and quinupristin/dalfopristin now available.2 Loffler and Macdougall2 have also highlighted the potential

Author’s reply:

Sir,

We would like to thank Doctor Neogi and his colleagues for their interest in our paper. We appreciate their concurrence of following guidelines for both the antimicrobial and surgical management of MRSA infections. The worldwide variation of MRSA isolates requires regional consideration in its management and we agree that tuberculosis compounds this dilemma in developing countries.

The aim of the manuscript was to assess our management protocol in line with current strategies and provide recommendation accordingly; a comprehensive review of antimicrobial therapy was beyond the scope of our paper. We have advised the use of vancomycin with consideration of rifampicin and/or fusidic acid as adjuvant therapy in deep surgical site infection and implant infection. There is no doubt that the complexity in treating MRSA has been exacerbated through the emergence of community-acquired infections as well as vancomycin-resistant strains. Consequently, there needs to be continuing development of agents effective against this multi-drug-resistant organism with newer antibiotics such as daptomycin, tigecycline and quinupristin/dalfopristin now available.2 Loffler and Macdougall2 have also highlighted the potential


role of older agents including clindamycin and doxycycline in the treatment of MRSA infection. However, the ultimate decision on medical therapy should be formed with appropriate microbiological services, taking into account the pathogen’s sensitivity, available antimicrobials, and local policy.
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Surgical site infection with methicillin-resistant Staphylococcus aureus after primary total hip replacement

Sir,

We read with interest the article by Walls et al in the March 2008 issue entitled ‘Surgical site infection with methicillin-resistant Staphylococcus aureus after primary total hip replacement’, and would like to highlight some patient, surgical and methodological factors that were not detailed in this study.

Patient factors.

The methods report that the study sample was obtained from a series previously reported.2 This original paper details that “.... of the 1790 primary total hip replacements undertaken at the study hospital, 18 (1%) became infected with MRSA.” This recent paper reports just 15 patients. Were the remaining three lost to follow-up or excluded for some other reason?

Medical co-morbidities greatly affect surgical site infection rates. This study briefly lists the co-morbidities of the patient cohort, including rheumatoid arthritis, cancer and anaemia, three conditions in which there is a wide range of severity and inherent immunosuppressive potential.14-16 Further, patients with these conditions will undoubtedly be on several medications that may have an immunosuppressive profile.1 More detail of both the severity of the co-morbidities and medication would be informative.

Nutritional status is known to be a significant predisposing factor to deep joint infection.2-10 Similarly, obesity is another known risk factor of deep surgical infection11 not reported in this study. Were any anthropometric, immunological or biochemical indicators – all known tools to assess nutritional status12 - employed for the study?

Surgical factors.

There is no mention of length of operation. Longer surgical time is associated with an increased infection risk.13 There is conflicting evidence regarding the efficacy of surgical face masks and surgical hoods in reducing the bacteria contamination.14-16 What did the surgeons involved in this study wear?

Drains, despite being necessary in some particular clinical situations, are known to be associated with surgical site infection.17 Were drains routinely used for the surgery of these patients?

Methodological factors.

The components used to routinely diagnose surgical site infection are known to have a high inter-observer error.18 Was any assessment made of the inter-observer error in the diagnosis of superficial, deep or implant infection?

No results from the erythrocyte sedimentation rate or C-reactive protein investigations, mentioned in the methods, are documented. Both of these serological investigations have been shown to provide excellent diagnostic test information for establishing the presence or absence of infection following primary joint replacement surgery.19,20
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Author’s reply:

Sir,

We would like to thank Mr Rogers and Mr Little for their interest in our paper and we welcome the opportunity to clarify some issues that have been raised.

Our hospital is a regional referral centre with many patients followed up at satellite institutions; unfortunately, the data were incomplete at these centres for the three cases mentioned, and so they were not included in this analysis.
It is correct to consider patient and operative risk factors separately; however, the emphasis of this paper was to review management of MRSA surgical site infection when it actually occurs. We did mention that risk factors for MRSA colonisation and infection have already been reported, and we listed measures to aid reduction in infection rates. Patient factors include a past history of MRSA infection or colonisation, recent hospitalisation (<6 months), residence within long-term care facilities or in a community with high MRSA prevalence, presence of chronic wounds, presence of invasive medical devices, increasing age, malignancy and underlying disease.1-6

In our series, four cases (27%) with MRSA present on admission were admitted electively from the community and none had been hospitalised prior to their surgery. We believe this serves as further evidence of the increasing prevalence of MRSA in the community.1,2 A total of 11 of our cohort (73%) suffered concomitant medical conditions, with hypertension (55%) and rheumatoid arthritis (36%) the most common. As we reported, this information was obtained from a retrospective chart review and we did not routinely perform pre-operative assessments of nutritional status or severity of immunosuppression during this time. All patients were determined medically fit for primary hip replacement. Five patients (33%) required steroid treatment for conditions including rheumatoid arthritis, polymyalgia rheumatica and asthma. If immunosuppressive drugs cannot be stopped in the peri-operative period we suggest that prophylactic vancomycin should be considered.

Surgical helmets or face masks with surgical hoods were worn in all cases depending on the consultant surgeon’s preference, with no difference in infection rates determined. Drains were also inserted in all cases during this period and routinely removed at 48 hours. While there is no agreement in the literature on the use of drains following hip surgery, a recent study of 1207 hip arthroplasties did not find the use of drains to be associated with an increased incidence of peri-prosthetic infection.8,9 Similar discrepancy exists regarding the relationship between operative time and post-operative infection.8,10 Therefore, larger multicentre studies are needed to provide the statistical power for multivariate analysis to determine which individual factors increase the risk of MRSA surgical site infection.

We consider the guidelines of the Centre for Disease Control, which have been widely accepted and used for reporting infection rates, to outline the criteria for surgical site infection correctly.10-12 The paper highlighted by Mr Rogers only reported discrepancies with some components of the diagnostic criteria for superficial surgical site infection and was performed by two clinicians and two nurses with varying levels of experience.13

We used inflammatory markers (ESR and CRP) to aid diagnosis and to monitor MRSA infection resolution. It can be difficult to differentiate early infected from non-infected cases as there is invariably a post-operative rise in both markers following hip surgery which may take several weeks to return to normal levels.14 MRSA is a highly virulent pathogen, reflected in our series with most surgical site infections presenting early, and compounds the interpretation of high early post-operative levels. It is more appropriate to review serial tests as infected cases tend to have persistently elevated levels.14 Furthermore, conditions that may cause an abnormal rise of ESR and CRP include inflammatory disorders and malignancy;15 such comorbidities affected six patients (out of 13) in our series. We therefore considered it inappropriate to report peak/pre-operative levels in this paper. However, we have discussed, where appropriate, normalisation of markers in relation to our management at all levels of surgical site infection supporting successful MRSA eradication.

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