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Accelerated surgery versus standard care in hip fracture (HIP ATTACK): An international, randomised, controlled trial

The HIP ATTACK Investigators

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SUMMARY

Background: Observational studies have suggested that accelerated surgery is associated with improved outcomes in patients with a hip fracture. The HIP ATTACK trial assessed whether accelerated surgery could reduce mortality and major complications.

Methods: We randomised 2970 patients from 69 hospitals in 17 countries. Patients with a hip fracture that required surgery and were ≥45 years of age were eligible. Patients were randomly assigned to accelerated surgery (goal of surgery within 6 hours of diagnosis; 1487 patients) or standard care (1483 patients). The co-primary outcomes were 1.) mortality, and 2.) a composite of major complications (i.e., mortality and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding) at 90 days after randomisation. Outcome adjudicators were masked to treatment allocation, and patients were analysed according to the intention-to-treat principle; ClinicalTrials.gov, NCT02027896.

Findings: The median time from hip fracture diagnosis to surgery was 6 hours (interquartile range [IQR] 4-9) in the accelerated-surgery group and 24 hours (IQR 10-42) in the standard-care group, p<0.0001. Death occurred in 140 patients (9%) assigned to accelerated surgery and 154 patients (10%) assigned to standard care; hazard ratio (HR) 0.91, 95% CI 0.72-1.14; absolute risk reduction (ARR) 1%, 95% CI -1-3%; p=0.40. The primary composite outcome occurred in 321 patients (22%) randomised to accelerated surgery and 331 patients (22%) randomised to standard care; HR 0.97, 95% CI 0.83-1.13; ARR 1%, 95% CI -2-3%; p=0.71.

Interpretation: Among patients with a hip fracture, accelerated surgery did not significantly lower the risk of mortality or a composite of major complications compared to standard care.

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INTRODUCTION

Worldwide, >1.5 million adults suffer a hip fracture each year.[1] Non-surgical management of a hip fracture is associated with a low probability of remaining ambulatory and an increased risk of chronic pain and mortality.[2,3] In high-income countries, approximately 95% of hip fractures are managed surgically.[4,5] Patients undergoing hip fracture surgery have higher risk-adjusted mortality and major complications than patients undergoing elective total hip replacement surgery, suggesting hip fractures, independent of surgery, increase patients' risks.[6]

Patients who suffer a hip fracture are at substantial risk of major complications (i.e., cardiovascular, infectious, bleeding, and neuro-cognitive) and mortality.[7-9] Observational studies suggest that accelerated surgery for a hip fracture is associated with a lower risk of mortality and major complications.[10,11] Hip fractures result in pain, bleeding, and immobility, and activate inflammatory, hypercoagulable, catabolic, and stress states that can precipitate medical complications.[12-15] Accelerated surgery will reduce the time patients are exposed to these harmful states and therefore may reduce the risk of medical complications and mortality. We undertook the *HIP* fracture *A*ccelerated surgical *T*rea*T*ment *A*nd *C*are trac*K* (HIP ATTACK) trial to determine whether accelerated surgery for hip fracture was superior to standard care in reducing death or other major complications.

METHODS

Study design, patients, and patient engagement

We undertook this investigator-initiated, randomised, controlled trial at 69 hospitals in 17 countries (i.e., Canada, Spain, India, Pakistan, South Africa, Italy, Poland, United Kingdom, United States, Malaysia, Belgium, France, Thailand, Netherlands, China, Hong Kong, Colombia). We have previously reported details of the trial design and methods.[16,17] Study

personnel recruited patients from March 14, 2014 to May 24, 2019. Before commencing recruitment, all centres obtained ethics approval, and the relevant health authorities approved the protocol.

Eligible patients were ≥45 years of age and diagnosed during regular working hours with a low-energy mechanism hip fracture that required surgery. Centres defined their study hours based on the local regular working hours. We excluded patients taking a therapeutic-dose of an anticoagulant for which no reversing agent was available, with a history of heparin induced thrombocytopenia if they were taking a therapeutic-dose vitamin K antagonist, with a peri-prosthetic or open fracture, with bilateral fractures, requiring an emergency surgery for another reason (e.g., subdural hematoma), refusing consent, or previously enrolled in HIP ATTACK.

Our approach to patient engagement was guided by the Canadian Institutes of Health Research (CIHR) Strategy for Patient-Oriented Research Patient Engagement Framework.[17] Patients were involved in trial governance auditing and provided input on the importance of the trial outcomes.

Randomisation and masking

Patients were randomly assigned (1:1) to accelerated surgery (i.e., goal of surgery within 6 hours of hip fracture diagnosis) or standard care. Our objective with accelerated surgery was to facilitate surgery as quickly as possible. We selected a goal of 6 hours because we knew this was a substantial improvement beyond standard care and achieving this target was feasible, based on the HIP ATTACK pilot. After obtaining consent from the patient or substitute decision maker, research personnel randomised patients through a central computerised randomisation system using randomly varying block sizes. Study personnel and investigators were unaware of

the block sizes. Randomisation was stratified by centre and type of planned surgery (i.e., arthroplasty or open reduction and internal fixation). Patients, healthcare providers (e.g., physicians undertaking preoperative medical clearance, anaesthesiologists, surgeons), and study personnel were aware of patients' allocated treatment assignment. Outcome adjudicators were masked to treatment allocation.

Procedures

Patients randomised to accelerated surgery underwent medical clearance by physicians who were available to rapidly evaluate these patients. After obtaining medical clearance, these patients moved into the next orthopaedic elective or trauma operating room slot (i.e., they were prioritised over elective cases and other non-emergent trauma cases). Any displaced elective cases were moved to the subsequent slot and, to avoid cancellation of any moved elective cases, when needed an extra operating room slot was facilitated at the end of the day. Patients randomised to standard care underwent medical clearance and were waitlisted for surgery according to local standard practices. All patients in the accelerated-surgery and standard-care groups underwent medical assessment and clearance before surgery. The difference between the groups was that a physician was available to undertake rapid medical assessment of patients in the accelerated-surgery group, whereas patients in the standard-care group were seen and medically cleared by a physician according to standard-care timelines (i.e., their medical assessment was not expedited).

All patients received the same structured follow-up for outcomes. For the first 7 days after randomisation, patients had daily troponin measurements and were assessed for delirium

with the confusion assessment method (CAM).[18] Patients were followed in hospital and contacted at 30 and 90 days after randomisation to determine trial outcomes.

Outcomes and adjudication

The co-primary outcomes were 1.) mortality and 2.) a composite of major complications (i.e., mortality and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding) at 90 days after randomisation. The Appendix presents secondary and tertiary outcomes and all outcome definitions. Trained physicians, masked to the treatment allocation, adjudicated the following outcomes: myocardial infarction, myocardial injury not fulfilling the definition of myocardial infarction, congestive heart failure, non-fatal cardiac arrest, stroke, pulmonary embolism, deep vein thrombosis, pneumonia, sepsis, and bleeding. Adjudicated events were used for the analyses.

Trial Monitoring

Monitoring in HIP ATTACK consisted of central data consistency checks, statistical data monitoring, and site monitoring. Site monitoring occurred at hospitals that randomised ≥40 patients or stood out on central data consistency checks or statistical data monitoring. For site monitoring, the study statistician randomly selected participants with and without primary outcomes, and independent monitors audited their hospital charts and supporting documents. Site monitoring occurred at 26 hospitals that randomised 76% of the trial patients. Study personnel corrected any data errors identified through central data consistency checks or site monitoring. Central data consistency checks and statistical monitoring raised concerns regarding

3 centres that had major issues during site monitoring. Data from these sites (total of 65 patients) were removed and further details are provided in the Appendix.

Statistical considerations

HIP ATTACK was originally designed to randomise 1200 patients, and the primary outcome was time to a composite of major complications at 30 days of follow-up. At an Investigator Meeting in April 2017, without knowledge of the trial results, a decision was made to increase the sample size to 3000 patients with 2 co-primary outcomes of mortality and a composite of major complications at 90 days of follow-up. This increase in sample size was needed to provide adequate power for the new co-primary outcome of mortality. For the comparison of accelerated surgery versus standard care, a sample size of 3000 patients provided the following: 88% power to detect a hazard ratio (HR) of 0.70 (2-sided α=0.0400) for mortality, assuming a standard-care group mortality rate of 13%; and 99% power to detect a HR of 0.70 (2-sided α=0.0150) for the composite of major complications, based on 45% overlap between the two co-primary outcomes and assuming a standard care group major complications rate of 30%.

The Independent Trial Monitoring Committee reviewed the data when 50% of the patients had completed 30 days of follow-up based on the initial sample size of 1200 patients, and when 50% and 75% of the patients had completed 90 days of follow-up based on the final sample size of 3000 patients. The committee used a modified Haybittle-Peto rule of 4 standard deviations (SDs) (α=0.0001) for analyses when 50% of the patients had completed follow-up and 3 SDs (α=0.00047) for the analysis when 75% of patients had completed follow-up.

The Operations Committee wrote and finalized the statistical analysis plan before analyses were undertaken or any investigators were unmasked to trial results. Patients were

analysed in the groups to which they were randomised (i.e., based on the intention-to-treat principle), regardless of the timing of their surgery. Patients lost to follow-up without having had the outcome of interest were censored on the last day their outcome status was known.

For the co-primary outcomes, we used Cox proportional hazards models to estimate the effect of accelerated surgery versus standard care, with stratification based on the type of planned surgery (i.e., arthroplasty versus open reduction and internal fixation). For the co-primary outcomes, we also plotted event rates over time using Kaplan-Meier methodology and used the log-rank test to determine p values.

The co-primary analyses were based on a fallback procedure such that if the first co-primary outcome (i.e., time to death) was significant at $\alpha=0.0400$, then the alpha would be unused and passed to the second co-primary outcome (i.e., time to a major complication), which would then be evaluated at $\alpha=0.05$.[19] If the first co-primary outcome was found to be non-significant, the second co-primary outcome would be evaluated at $\alpha=0.0150$. With the fallback hierarchical testing procedure, the type I error rate is partitioned among the co-primary outcomes in an order determined *a priori*; if the first hypothesis is rejected, the type I error rate can be accumulated, thus preserving the family-wise type I error rate.[19]

Secondary and tertiary binary events with an event date were analysed using an approach similar to that of the primary outcomes. For secondary and tertiary outcomes that were binary events but without an event date (e.g., new residence in a nursing home), logistic regression was undertaken to estimate the effect of accelerated surgery versus standard care, and a χ^2 test was used to calculate the p value.

For the co-primary outcomes, we performed the following 2 prespecified subgroup analyses: 1.) patients who presented to the hospital <4 hours after their hip fracture, ≥4-24 hours

after their hip fracture, versus >24 hours after their hip fracture; and 2.) patients who had, versus did not have, an acute severe medical condition (Appendix) after their hip fracture but before randomisation. We expected a larger relative treatment effect in patients who presented earlier after their fracture and a smaller treatment effect in patients who had acute severe medical conditions after their fracture but before randomisation. We used Cox proportional hazards models that incorporated tests of interaction, designated as significant if $p<0.05$.

All analyses were performed in SAS®, version 9.4. This trial was registered with ClinicalTrials.gov, number NCT02027896.

Trial coordination and role of the funding sources

The study was funded by grants from the CIHR, the Ontario Strategy for Patient Oriented Research Support Unit, the Ontario Ministry of Health and Long-Term Care, the Hamilton Health Sciences Foundation, Physicians' Services Incorporated Foundation, Michael G. DeGroote Institute for Pain Research and Care, Smith & Nephew (to recruit patients in Spain), and Indiegogo Crowdfunding. The Population Health Research Institute was the trial coordinating centre and was responsible for the randomisation system, maintenance of the database, data monitoring, analyses, and study-centre coordination. The funders of the trial had no role in data collection, data analyses, data interpretation, or writing of the manuscript. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

RESULTS

We randomised 2970 patients to receive accelerated surgery (n=1487) or standard care (n=1483). Fifteen patients (<1%) were lost to follow-up after hospital discharge (Figure 1). The baseline characteristics and details of surgery were similar between groups (Table 1). Among participants, the mean age was 79 years, 69% were women, 33% needed help with activities of daily living, 22% had diabetes, 18% had dementia, and 18% resided in a nursing home before their hip fracture. The most common types of fractures were intertrochanteric (52%) and femoral neck (44%). The surgeries performed were open reduction and internal fixation in 63% of participants and arthroplasty in 35%.

The timelines from hip fracture to randomisation were similar between the 2 groups (Table 2). The median time from hip fracture to hospital arrival was 3 hours (interquartile range [IQR], 1-15), and the median time from hospital arrival to randomisation was 3 hours (IQR, 2-5). The median time from hip fracture diagnosis to medical clearance was 2 hours (IQR, 1-4) in the accelerated-care group and 4 hours (IQR, 2-13) in the standard-care group, $p<0.0001$. The median time from hip fracture diagnosis to surgery was 6 hours (IQR, 4-9) in the accelerated-surgery group and 24 hours (IQR, 10-42) in the standard-care group; median absolute difference of 18 hours (95% confidence interval [CI] 17-19), $p<0.0001$.

Death occurred in 140 patients (9%) assigned to accelerated surgery and 154 patients (10%) assigned to standard care; HR 0.91, 95% CI 0.72-1.14; absolute risk reduction (ARR) 1%, 95% CI -1-3%; p=0.40, (Table 3, Figure 2). A major complication occurred in 321 patients (22%) randomised to accelerated surgery and 331 patients (22%) randomised to standard care; HR 0.97, 95% CI 0.83-1.13; ARR 1%, 95% CI -2-3%; p=0.71. Post-hoc random-effects Cox models that adjusted for potential site-clustering effects produced similar results to the primary analyses (Supplemental Table 1).

Among the secondary outcomes, there were fewer strokes in patients randomised to accelerated surgery compared to standard care (5 patients [<1%] versus 14 patients [1%]; HR 0.35, 95% CI 0.13-0.97; p=0.0470) (Table 3). Post-hoc Fisher's exact test for stroke demonstrated p=0.0405. Delirium was less common in the accelerated-surgery group (132 patients [9%]) compared to the standard-care group (175 patients [12%]), odds ratio (OR) 0.72, (95% CI 0.58-0.92); ARR 3%, 95% CI 1-5%. Fewer patients randomised to accelerated surgery compared to standard care had an infection without sepsis (170 patients [11%] versus 207 patients [14%]; HR 0.80, 95% CI 0.65-0.98). Fewer patients had a urinary tract infection in the accelerated-surgery group compared to the standard-care group (120 patients [8%] versus 150 patients [10%]; HR 0.78, 95% CI 0.61-0.99; ARR 2%, 95% CI <1-4%) (Supplemental Table 2).

For the tertiary clinical outcomes, including 5 orthopaedic outcomes (i.e., hip re-operation, prosthetic hip dislocation, implant failure, peri-prosthetic fracture, and surgical site infection), there were no significant differences between the randomised groups (Supplemental Table 3). Patients allocated to accelerated care were faster to mobilise after randomisation compared to patients allocated to standard care (25 hours [IQR, 21-45] versus 46 hours [IQR, 31-71]; absolute median difference 21 hours; 95% CI 20-22; p<0.0001) (Supplemental Table 4). The mean time from randomisation to hospital discharge was 10 days in the accelerated-surgery group and 11 days in the standard-care group; absolute mean difference 1 day (95% CI 1-2; p<0.0001).

Patients randomised to accelerated surgery stood up and were able to fully weight bear earlier than patients randomised to standard care (absolute median difference 21 hours, 95% CI 18-24; and 26 hours, 95% CI 21-30, respectively) (Supplemental Table 5). Post-hoc analyses demonstrated that more patients randomised to accelerated care were discharged ≤10 days after

237 randomisation, whereas more patients randomised to standard care stayed 11-20 days and >20
238 days from randomisation to hospital discharge (Supplemental Table 6).

239 The effects on mortality did not differ across the prespecified subgroups (Figure 3). For
240 the co-primary outcome of major complications, the subgroup analysis based on time from hip
241 fracture to hospital arrival demonstrated a significant interaction (p=0.0198). This subgroup
242 analysis demonstrated that the HR for major complications decreased as the time from hip
243 fracture to hospital arrival increased.

244 Subgroup analyses for the co-primary outcomes based on an expanded list of acute
245 medical conditions (Appendix), broader than the pre-specified subgroup, demonstrated the
246 effects were consistent across the subgroups (Supplemental Figure 1). Post-hoc subgroup
247 analyses for the co-primary outcomes based on whether patients had an elevated troponin
248 measurement before randomisation demonstrated a statistically significant interaction (p=0.0076)
249 for mortality (Supplemental Figure 2). These analyses suggested patients with an elevated
250 troponin measurement at baseline had a lower risk of mortality with accelerated surgery
251 compared to standard care (17 deaths among 174 accelerated-surgery patients [10%] versus 42
252 deaths among 175 standard-care patients [24%]; HR 0.38, 95% CI 0.21-0.66).

253 Post-hoc subgroup analyses for the co-primary outcomes, based on the type of fracture
254 (i.e., intertrochanteric versus femoral neck) and separately based on the type of surgery (open
255 reduction and internal fixation versus arthroplasty), demonstrated that the effects were consistent
256 across the subgroups (Supplemental Figure 3 and 4, respectively). Post-hoc analyses for the co-
257 primary outcomes based on patients' age (i.e., 45-64, 65-84, and ≥85 years) demonstrated the
258 effects were consistent across the subgroups (Supplemental Figure 5).

The day after randomisation, patients in the accelerated-surgery group had a lower pain score than patients in the standard-care group (Supplemental Table 7). Fewer patients in the accelerated-care group had moderate to severe pain on days 4-7 after randomisation, compared to patients in the standard-care group (Supplemental Table 8).

DISCUSSION

Statement of principal findings

Accelerated surgery did not reduce the risk of the co-primary outcomes of mortality and a composite of major complications, compared to standard care. Accelerated surgery compared to standard care resulted in a lower risk of delirium (OR 0.72, 95% CI 0.58-0.92), urinary tract infection (HR 0.78, 95% CI 0.61-0.99), and moderate to severe pain on days 4-7 after randomisation. Accelerated surgery also resulted in faster mobilisation after randomisation (absolute median difference, 21 hours; 95% CI 20-22), and a shorter time from randomisation to hospital discharge (absolute mean difference, 1 day; 95% CI 1-2).

Our trial in relation to other studies

A systematic review and meta-analysis of risk-adjusted *observational* data demonstrated, irrespective of the cut-off defining delayed surgery (24, 48, or 72 hours), earlier surgery (i.e., within the cut-off time) was associated with a significantly lower risk of mortality (4208 patients, 721 deaths; relative risk 0.81, 95% CI 0.68–0.96).[10] Risk adjusted observational studies have demonstrated that surgery within 12 hours of a hip fracture diagnosis was associated with a lower risk of mortality.[11,20,21] Although these observational studies undertook risk-adjusted

analyses, observational studies remain at risk of confounding by indication and residual confounding.

Two small trials randomised patients with a hip fracture to accelerated surgery versus standard care. One trial randomised 71 patients with a hip fracture to early surgery or standard care; median time to surgery was 1 day versus 2 days, respectively.[22] The investigators reported that patients allocated to early surgery had a shorter length of hospital stay compared to patients allocated to standard care (21 versus 33 days; relative risk [RR] 0.48, 95% CI 0.27-0.85). HIP ATTACK also showed that accelerated surgery had a reduced time from randomisation to hospital discharge. The HIP ATTACK pilot randomised 60 patients to accelerated surgery or standard care with median times from diagnosis to surgery of 6 versus 24 hours, respectively.[7] In this pilot 4 patients randomised to accelerated surgery and 9 patients randomised to standard care developed delirium. These results were consistent with the HIP ATTACK trial.

Interpretation

Despite surgery being performed at a median time of 6 hours after the hip fracture diagnosis in the accelerated-surgery group versus a median of 24 hours in the standard-care group (median absolute difference of 18 hours, 95% CI 17-19), there was no significant effect of accelerated surgery on mortality (HR 0.91, 95% CI 0.72-1.14) or major complications (HR 0.97, 95% CI 0.83-1.13). Accelerated surgery did, however, demonstrate a reduction in delirium (OR 0.72, 95% CI 0.58-0.92, ARR 3%, 95% CI 1-5%), urinary tract infection (HR 0.78, 95% CI 0.61-0.99, ARR 2%, 95% CI, <1-4%), and moderate to severe pain on days 4-7 after randomisation. The ARR for delirium and urinary tract infection represent effects that patients are likely to consider important.

Accelerated surgery may have reduced the risk of delirium by reducing urinary tract infection, reducing moderate to severe pain, and having patients mobilise, stand, and weight bear more rapidly than patients randomised to standard care. In patients presenting with a hip fracture, to avoid the discomfort associated with using a bedpan to urinate, it is common practice to insert a Foley catheter. These catheters are usually not removed until after surgery, when patients start to mobilise. That patients randomised to accelerated surgery underwent surgery 18 hours earlier and mobilised 21 hours earlier than patients randomised to standard care may explain how accelerated surgery reduced the risk of urinary tract infection. Although patients allocated to accelerated surgery demonstrated a lower risk of stroke, we offer cautious interpretation of this finding. In contrast to delirium (307 events) and urinary tract infection (270 events), there were only 19 strokes and this result has a fragility index of 2 (i.e., only 2 patients in the accelerated-care group would have to change from not having a stroke to having a stroke to reverse statistical significance).[23]

The mean time from randomisation to hospital discharge was 10 days in the accelerated-surgery group and 11 days in the standard-care group; absolute mean difference 1 day (95% CI 1-2; $p<0.0001$). Given the cost associated with spending an extra day in the hospital, this represents an important difference. Several points support the credibility of this finding: 1.) the coherence of the data across outcomes – patients randomised to accelerated surgery had surgery 18 hours earlier, mobilized 21 hours earlier, stood 21 hours earlier, and achieved full weight bearing 26 hours earlier, compared to patients randomised to standard care; one would anticipate that patients who mobilize, stand, and weight bear more quickly will also be discharged earlier; 2.) more patients randomised to accelerated care were discharged ≤10 days after randomisation, whereas more patients randomised to standard care stayed 11-20 days and >20 days from

randomisation to hospital discharge (Supplemental Table 6); and 3.) prior data from a small trial supports this finding.[22] Of our two *a priori* subgroup analyses, one demonstrated a statistically significant interaction p value (i.e., for the composite outcome based on time from hip fracture to hospital arrival) (Figure 3). Although a significant interaction p value suggests the differences in treatment effects are beyond what would be expected based on chance and supports the credibility of a subgroup effect, the observed direction of effect was the opposite of our stated *a priori* hypothesis (i.e., we expected a larger treatment effect in patients who present within shorter time periods of their hip fracture, whereas we observed the opposite), which substantially lowers the credibility that this represents a real subgroup effect.[24,25]

Some authors have cautioned that accelerated surgery for a hip fracture may negatively impact patients' outcomes by preventing or limiting the opportunity to optimize patients' medical conditions before surgery;[26,27] however, our subgroup analysis based on acute medical conditions does not support this concern (Figure 3, Supplemental Figure 4). Moreover, our post-hoc subgroup analysis suggested patients with an elevated troponin measurement at baseline had a lower risk of mortality with accelerated surgery compared to standard care (HR 0.38, 95% CI 0.21-0.66). An elevated baseline troponin measurement in patients with a hip fracture may identify patients who are not tolerating the physiological stress associated with the hip fracture, and these patients may benefit from accelerated surgery.

Waiting for hip fracture surgery is undesirable. When patients sustain a hip fracture, they are forced to lie flat in a bed and are either in pain or needing analgesic medications, which often have side effects. Moreover, patients usually have to fast while waiting for surgery and many will get a urinary catheter, which will only be removed after surgery. That <5% of eligible

patients declined to participate in the HIP ATTACK trial provides evidence that patients want accelerated surgery.

HIP ATTACK further provides evidence of the safety and benefits (e.g., reduced risk of delirium and more rapid mobilisation) of accelerated surgery compared to standard care. Lack of operating room time and medical clearance are the main barriers to accelerated surgery.[28,29] We demonstrated in HIP ATTACK that it is possible to overcome these barriers. Patients randomised to accelerated surgery went into the next orthopaedic elective or trauma operating room slot and any displaced elective cases were moved to the subsequent slot. To avoid cancelling any elective cases, when needed, an extra operating room slot was facilitated at the end of the day. This represents the main cost to centres to facilitate accelerated surgery. This cost along with the cost savings from discharging a patient home a day earlier will help inform the economics of accelerated surgery. We plan to publish formal economic analyses related to the HIP ATTACK data. Moreover, we will publish the 1-year results, after all patients have completed the 1-year follow-up.

HIP ATTACK included patients ≥45 years of age, and the trial does not inform the effect of accelerated surgery on younger patients. Patients <45 years of age are, however, commonly excluded from perioperative trials because of their lower risk of postoperative complications.[30-32] Moreover, it is uncommon for patients <45 years of age to suffer a low-energy mechanism hip fracture.

Strengths and limitations

HIP ATTACK is the first large randomised trial to inform the effects of accelerated surgery compared to standard care. We obtained follow-up on >99% of participants. HIP

ATTACK has limitations. Three centres had major data quality issues, and we had to remove these centres and their 65 randomised patients from the trial. Although this resulted in our trial falling just short of our intended sample size (i.e., 2970 patients instead of 3000), this did not have a meaningful impact on power. Despite variation in the time from hip fracture diagnosis to surgery in our standard-care group, our results primarily inform the effects for patients who went to surgery a median of 6 versus 24 hours after their hip fracture was diagnosed. Observational data, clinical experience, and biological rationale suggest that the longer a patient is immobile and lying in a bed the higher the risk of poor outcomes.[2] Therefore, our findings do not preclude different results in centres with standards of care that take substantially longer to get patients into surgery than the standard-care group in HIP ATTACK.

We did not collect data on the orthopaedic outcomes of non-union or malunion; however, accelerated surgery had no effect on the 5 orthopaedic outcomes we did evaluate (Supplemental Table 3). We did not collect data on the timing of urinary catheter removal following surgery. We expected a standard-care group mortality rate of 13% but it was 10% and a major complications rate of 30% but it was 22%. Considering the 95% CIs around their associated treatment effects, there is still the possibility of a 28% relative risk reduction (RRR) for mortality and a 17% RRR for major complication. We only included patients diagnosed during regular working hours. Given that after regular working hours, there tend to be fewer healthcare providers in hospitals and those providers may be more fatigued, understanding the effects of accelerated surgery outside of regular working hours will require its own trial. We did not collect data on the seniority of surgeons, anaesthesiologists, and physicians. Although physician skill level may vary across sites and may affect outcomes, randomisation was stratified by centre to minimize any such impact on the effects of the study treatment groups.

Conclusions

Among patients with a hip fracture, accelerated surgery did not lower the risk of mortality or a composite of major complications compared to standard care. It did, however, reduce the risk of delirium, urinary tract infection, and moderate to severe pain, and resulted in faster mobilisation, standing, weight bearing, and hospital discharge.

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DECLARATION OF INTERESTS

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Data Sharing Statement: The Population Health Research Institute (PHRI) is the sponsor of this trial. The PHRI believes the dissemination of clinical research results is vital and sharing of data is important. PHRI prioritizes access to data analyses to researchers who have worked on the trial for a significant duration, have played substantial roles, and have participated in raising the funds to conduct the trial. PHRI balances the length of the research study, and the intellectual and financial investments that made it possible with the need to allow wider access to the data collected. Data will be disclosed only upon request and approval of the proposed use of the data by a Review Committee. Data are available to the journal for evaluation of reported analyses. Data requests from other non-HIP ATTACK investigators will not be considered until 5 years after the close out of the trial.

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