ORIGINAL ARTICLE

Unstable pelvic ring injury with hemodynamic instability: What seems the best procedure choice and sequence in the initial management?

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KEYWORDS
Pelvic unstable fracture; Polytrauma; External fixation; Packing

Summary

Introduction: Most fatalities related to pelvic ring injuries occur early and are caused by massive retroperitoneal bleeding. The objective of our study is to determine the optimal sequence of surgical procedures to restore hemodynamic stability in patients with unstable pelvic ring injuries.

Patients and methods: This was a retrospective review of all patients with pelvic fractures and hemodynamic instability admitted to our level 1 trauma center between January 1998 and December 2008. We entered into our polytrauma database the following patient characteristics: age, sex, mechanism of injury, Injury Severity Score (ISS), classification of injury, timing of operative intervention, and type of operative procedures. Patients were divided into four groups (according to the sequence of surgical procedures performed within 24 hours following admission), as follows: group 1: patients treated with external fixation only; group 2: patients receiving external fixation followed by angiography; group 3: patients receiving external fixation followed by laparotomy and angiography; and group 4: patients treated by immediate laparotomy or angiography before skeletal fixation.

Results: Eighty of 136 patients admitted with a pelvic fracture were classified, as unstable AO/OTA type B or C pelvic ring injury, and 70/80 were hemodynamically unstable. Eight patients died shortly after arrival and two remained stable without requiring any early procedure. Sixty patients went immediately to the operating room. Twenty-nine patients were placed in group 1 with 100% survival, 12 in group 2 with 91% survival, 11 in group 3 with 82% survival, and eight patients placed in group 4 with 0% survival ($P < 0.001$).

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Conclusions: The management of hemorrhagic instability linked to pelvic ring disruption involves a sequence of therapeutic events, which is more important than the events themselves. Pelvic bone stabilization by pelvic clamp or external fixator followed by arteriography seems to be the more secure. Angiographic embolization is the method of choice whenever haemodynamic instability coexists with an unstable pelvic disruption. Laparotomy and packing are restricted to extreme cases in remote hospitals with skillful surgeons! Actually aortic balloon is a good solution to control uncontrollable bleeding. Level of evidence: Level IV. Retrospective study.

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Introduction

Unstable pelvic ring injuries are present in more than 25% of all polytraumatized patients [1,2], and are the cause of early death in one of every three such patient [3,4]. Most fatalities related to pelvic ring injuries are caused by retroperitoneal bleeding and occur during the hours following trauma. The amount of retroperitoneal pelvic bleeding depends upon the location of the pelvic disruption and the amount of initial displacement. Low-pressure bleeding is present in a vast majority of patients and occurs at the exposed fracture surfaces or at torn veins, as opposed to the less frequent high-pressure arterial bleeding. Mears and Rubash [5] showed that a gap of only 3 cm at the pubic symphysis does increase the volume of the pelvis as much as 1.5 liters. Local compression or tamponade can only take place and control the expansion of retroperitoneal hematomas if skeletal stability is restored. Tamponade is mostly effective against low-pressure bleeding. High-pressure bleeding is less controllable by tamponade [6–8].

Initial treatment of trauma patients at the accident scene relies upon established Advanced Trauma Life Support (ATLS) principles. The early, on-site application of pelvic binders to victims presenting with clinical signs of pelvic instability has been shown to efficiently prevent pelvic volume increase and provide temporary haemodynamic stability [9]. Paramedic teams throughout the world are trained and equipped to implement this simple life-saving procedure. Upon admission to the emergency department, patients with pelvic ring injuries who remain haemodynamically unstable despite resuscitation efforts should be transferred immediately to the operating room for surgical stabilisation. The fact that patients with unstable pelvic ring injuries and associated haemodynamic instability or open pelvic fractures require immediate and aggressive surgical care is undisputed. However, controversy remains concerning the choice as well as sequence of the life-saving surgical procedures required.

Schematically, four procedures are available to acutely control pelvic bleeding in severely hypotensive patients: immediate skeletal external fixation (Fixex or pelvi-clamp), direct vessel ligation, angiographic embolization which may control high-pressure arterial bleeding; and retroperitoneal pelvic packing to help control both high-pressure as well as low-pressure bleeding. Low-pressure pelvic bleeding is present in more than 85% of pelvic fractures [10,11]. This may explain the good hemostatic efficiency of mechanical stabilization and tamponade unanimously recommended in the modern literature. Over the last 15 years the haemodynamic efficiency of external pelvic fixation devices such as the pelvic C-clamp [12] has been well documented. The application of external pelvic fixators or C-clamps is a quick and minimally invasive procedure, which does not prevent nor delay an optional subsequent laparotomy or angiographic procedure. The old controversy as to which specialist; visceral surgeon, orthopaedic surgeon, radio-angiologist, should act first is less actual nowadays. However, experience shows that in stressful situations involving severe haemodynamic instability, these teams did in fact not always agree regarding which procedure should have priority, despite a growing literature supporting the application of skeletal fixation prior to any subsequent surgical or angiographic procedure [13,14].

In the modern literature, the ideal sequence of actions required if some degree of haemodynamic instability remains following initial external pelvic ring fixation is still the subject of animated debates. Should angiography with embolization follow? Such an approach is supported by many, particularly in North America. Others, particularly as noted in the north-European literature, favour retroperitoneal pelvic packing and direct arterial bleeding control.

The goal of this retrospective study, based upon the experience of a university hospital trauma center, is to determine the best sequence of events to control pelvic bleeding with or without associated intraperitoneal bleeding, and to identify the optimal sequence effectiveness in the management of haemodynamically unstable patients with unstable pelvic ring injuries. We argue to prevent crash-laparotomy in emergency but to manage pelvic fractures with a “team” spirit.

Methods

From January 1998 until December 2008, all patients admitted to our level 1 trauma center with a pelvic were prospectively entered into our polytrauma database. Pelvic ring injuries were classified on the initial AP pelvic plain film according to the AO/OTA and patients presenting with type 61-B or 61-C lesions were identified [15]. From this subgroup we identified those patients who presented with haemodynamic instability, defined as a combination of the following criteria: Hypovolemic shock; estimated blood loss greater than 1500 mL (≥ 30%); tachycardia; hypotension (≤ 90 mmHg systolic BP); and delayed capillary refill greater or equal to 2 seconds. Most patients had been brought to the emergency department equipped with either a pelvic binder or similar strap-belt placed by the paramedic team at the accident scene. Following admission patients were assessed and
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managed in accordance with ATLS guidelines. Relevant expertise from visceral and orthopaedic surgeons, urologic surgeons, neurosurgeons, cardiothoracic surgeons and radiologists, as well as computed tomography (CT), was available within minutes in the emergency department. No surgical procedures were performed in the emergency department, but always took place a short distance away in the operating room devoted to emergency care. Interventional radiologists on call 24/7 were immediately requested by the emergency department as soon as an unstable hemodynamic situation involving pelvic trauma was identified. Thus they were able to make preparations for eventual angiographic procedures while the patient was still being treated in the operating room. Patient information including age, sex, mechanism of injury, ISS, type of injury, timing of investigations and surgical procedures were recorded prospectively in a specifically designed polytrauma database. The database was used to identify which patients had received pelvic external fixation, arteriography, and/or a laparotomy, and in which sequence. The goal was to define the sequence and timing of these different procedures and their effect upon patient outcome. Patients were divided into four groups according to the sequence of surgical procedures undertaken during the 24 hours following admission. Group 1 included patients treated with pelvic external fixation only. Group 2 included patients treated with a pelvic external fixator followed by angiography. Patients who received a pelvic external fixator followed by laparotomy and in some cases, additional angiography, were classified as Group 3. Patients who were treated by immediate laparotomy or angiography before eventual skeletal fixation were classified into group 4.

Results

During the study period 136 patients were admitted with a pelvic or acetabular fracture, of which 80 presented with an unstable type B or C pelvic ring injury. From this group of patients, 70 patients were hemodynamically unstable as per the criteria described above.

All sustained their injuries from high-energy trauma, either during a high-speed motor vehicle accident or a fall from a height. Of these 70 patients, eight died shortly after arrival in the emergency department despite resuscitation efforts, before any surgical hemostatic procedure could be attempted. Two patients remained stable with the pelvic strap binder and could be transferred directly to the ICU without requiring any early surgical or angiographic hemostatic procedure (Fig. 1).

The following surgical procedures were performed within the first 2 hours: pelvic external fixation was performed in 56 using an anterior external fixator frame (Fixex) \( n = 15 \), or pelvic C-clamp \( n = 41 \) (Table 1).

Into group 1, they were treated with external fixation alone and did not require laparotomy, retroperitoneal packing or arteriography during their course of treatment until their discharge. In group 2, patients were treated by immediate external fixation followed by angiography and embolization due to persisting haemodynamic instability.

Into group 3, two patients presented with an open pelvic wound, at the anterior abdominal wall in one and perineal in the other. All these patients underwent skeletal fixation followed by laparotomy. Retroperitoneal bleeding was observed in all these 11 patients. Although most presented with intraperitoneal tainted exsudate, fresh intraperitoneal blood was present in only 4. The precise source of the intraperitoneal bleeding was identified in only one patient as originating from the azygos vein and spleen. In the other 3, the bleeding was described as multilocular, thoraco-abdominal in one patient and originating from the retroperitoneum as well in the other two. Splenectomy was required in three patients, and in one patient, selective multiple arterial ligatures were performed under temporary aortic clamping. Additional haemostatic procedures involved immediate retroperitoneal packing for 48 hours in two patients and immediate angiography in four others. In this subgroup of four patients who could be transferred to angiography following initial external fixation and laparotomy, the average ISS was 75 (range 43–75), all patients survived. In the group of seven patients who underwent external fixation, followed by laparotomy without angiography, one patient died from crush syndrome and another one from massive aortic bleeding. The overall survival rate in group 3 was 82%. Results of this group suggest the high importance of angiography.

In group 4, the patients were treated by laparotomy (7 patients) or angiography (1 patient) prior to any skeletal fixation. In all these patients, the decision to proceed immediately with a so-called crash-laparotomy was taken under highly stressful circumstances, dealing with a patient who was judged “in extremis”, thus requiring immediate invasive measures. In these patients, the team in charge considered that the delay required for the application of an external pelvic fixator was not appropriate, and that the laparotomy should therefore occur immediately. All these eight patients died of haemorrhagic complications on the table or during attempted retroperitoneal packing or direct arterial hemostasis. In four of these eight, the fatal issue occurred despite the subsequent placement of a pelvic external fixator immediately following the laparotomy or angiography.

Discussion

Critical decisions must be made in the emergency department regarding the acute management of haemodynamically unstable patients with unstable pelvic ring injuries. A multidisciplinary approach is required, especially

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Table 1  Patient distribution and outcome according to the sequence of surgical events.

<table>
<thead>
<tr>
<th></th>
<th>Group 1a</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>First surgery</td>
<td>External fixation</td>
<td>EF + Angiography</td>
<td>EF + Laparotomy</td>
<td>Laparotomy first/Angio first</td>
</tr>
<tr>
<td>Number of patients</td>
<td>29</td>
<td>11</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Age (y)</td>
<td>43 (20–74)</td>
<td>39 (17–76)</td>
<td>36 (22–58)</td>
<td>39 (16–57)</td>
</tr>
<tr>
<td>ISS</td>
<td>46 (27–75)</td>
<td>56 (23–75)</td>
<td>67.5 (50–75)</td>
<td>59 (50–75)</td>
</tr>
<tr>
<td>Survival rate (%)</td>
<td>100</td>
<td>91</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>One year later</td>
<td>Day 2: cerebral trauma</td>
<td>Day 1: crush syndrome</td>
<td>8 patients on the operating table from haemorrhagic complication even with vascular direct approach and packing</td>
</tr>
<tr>
<td></td>
<td>6 months later: pulmonary infection</td>
<td></td>
<td>(neither of these patients underwent arteriography before laparotomy)</td>
<td></td>
</tr>
<tr>
<td>Remarks</td>
<td>Arteriography is preferred before laparotomy but after EF</td>
<td></td>
<td>Arteriography or intraaortic balloon is the best procedure but after EF</td>
<td></td>
</tr>
</tbody>
</table>

*a In groups 1, 2 and 3, external pelvic fixation occurred before further procedures. In group 4, crash-laparotomy was performed first, before eventual external fixation or angiography.

in situations where a strong suspicion of exsanguinating intra-abdominal bleeding exists. In the past, a crash-laparotomy with immediate retroperitoneal packing was considered a reasonable option in critically unstable patients. As shown in group 3, laparotomy was really useful in three cases (splenectomy) otherwise arteriography should be the best treatment. However, hemorrhage often proved to be problematic since the source of bleeding could not be identified and packing often proved inefficient to control retroperitoneal hemorrhage. Exposure of the pelvic cavity actually increased bleeding in many such patients [13]. It is essential to distinguish low-pressure bleeding from high-pressure bleeding. Low-pressure bleeding is always present in pelvic dislocations, and originates from torn veins or fractured bone surfaces. Significant high-pressure arterial bleeding, is less frequent. Either higher or allowing for low-pressure sources of bleeding may be life-threatening. External fixation, the tamponade effect to take place, is effective against low-pressure bleeding by restoring the pelvic volume within normal limits. The approximation of fracture surfaces may also play a role in this respect. Local compression, or tamponade, is not as efficient against high-pressure bleeding. Type B pelvic dislocations may be efficiently stabilized using a classical anterior frame, inserted into the iliac crest or supraacetabular area. In type C injuries, anterior frames are less adequate for posterior stabilization and pelvic C-clamp should be preferred. After a pelvic dislocation, the abdominal wall still provides some mechanical stability to the pelvic ring. Failure to stabilize the pelvic skeleton prior to a laparotomy will completely suppress this remaining stability and annihilate any remaining local tamponade, therefore increasing bleeding. This simple physiopathological fact is supported by biomechanical as well as clinical studies. In a cadaveric study, Grimm et al. [6] measured the volume of colloidal fluid infusion in simulated type B injuries. External fixation limited the volume of the retroperitoneal volume, whereas laparotomy without prior fixation annihilated the tamponade effect. In another cadaveric study using CT imaging, Ghanayem et al. showed that the volume of a disrupted pelvic ring was further increased by laparotomy due to the loss of the abdominal wall tension-band [16]. Pohlemann et al., in his classical description of retroperitoneal packing, showed that the application of the pelvic clamp before laparotomy did cut the rate of mortality in half [13]. The positive haemodynamic effects of skeletal stabilisation using quick and efficient devices such as the C-clamp is undisputed among traumatologists. This includes the proponents of retroperitoneal packing, who also recommend initial external fixation [10,14,17]. Low-pressure bleeding is the most frequent cause of pelvic bleeding. Damage controlling measures using external fixation alone, without any additional haemostatic measure, is therefore often sufficient to significantly reduce retroperitoneal bleeding. In one study reporting 14 haemodynamically unstable pelvic ring fractures requiring immediate external fixation, Sadri et al. finds that arterial embolization was needed in only five (36%) to restore hemodynamic stability [7]. In our present series, considering the patients who did not undergo laparotomy, only 12 patients out of 41 (29%) required subsequent angiographic intervention after skeletal fixation had been performed.

The application of a C-clamp or external fixator is a quick, minimally invasive, and straightforward procedure that does not delay or interfere with subsequent procedures such as laparotomy or angiography. Application of a pelvic external fixator, or C-clamp, does not require a high level of surgical skills and can usually be safely performed by a resident with 2 to 3 years of training. Our results, as other’s [10,13], confirm that skeletal fixation should be performed prior to any other procedure such as angiography or laparotomy. In our series, 49 out of 52 (94%) patients who received initial skeletal fixation were long-term survivors, as compared to none of the eight patients who did not have immediate skeletal

fixation prior to laparotomy [7] or angiography [1]. These results are in accordance with those of recent studies [18,19]. In a recent multicenter report on 217 patients by Verbeek et al., authors report a significantly higher haemorrhage-related mortality if laparotomy was performed either before other surgical measures or even as compared to no surgical procedure at all [20]. Intraperitoneal injuries are frequently associated with pelvic ring injuries with reported rates in the range of 30 to 50% [21–23]. The discovery of a significant amount of intraperitoneal fluid by CT or ultrasound is considered an indication for laparotomy and/or angiography.

Based upon our findings, as well as current literature consensus, one must however admit that the exact origin of intraperitoneal blood will not always be identified, since it may lie in the retroperitoneum or thorax. In a series of 31 patients with type B or C pelvic ring disruptions associated with significant intraperitoneal fluid, Rucholz et al. identified the source of bleeding as retroperitoneal in only one patient, in the other 30, the sources of intraperitoneal blood were often multiple and due to significant organic lesions requiring repair [24]. In our series, 18 patients underwent a laparotomy. Our intraabdominal findings included seven spleen lacerations, eight liver lacerations, four ileo-jejunal wounds, 13 urogenital lesions, one pancreatic tear and 1 inferior vena cava tear. In two patients, no intraperitoneal lesions could be found at exploration except for a retroperitoneal hematoma. Peritoneal pelvic packing is a rapid method for controlling retroperitoneal hemorrhage, and some authors [25] are of the opinion that it could replace the need for urgent angiography. The technique initially described by Pohlemann et al. [13] relies upon a limited lower midline or Pfannenstiel incision. Such a limited approach does not allow for exploration of the retroperitoneum or peritoneal space and minimizes the loss of stabilizing effect of the abdominal wall. However, pelvic packing remains an invasive procedure that in order to be life-saving must be carried out expeditiously and without attempts at precise identification of sources of bleeding. It requires a level of surgical expertise not always available (particularly during night shifts). Furthermore, if preperitoneal packing is not skillfully performed, the procedure may be harmful and as well compromise options for eventual future open reduction and internal fixation of the pelvic ring. Additionally, packing requires a second-look procedure for removal of the packing material. Our results substantiate the idea that retroperitoneal packing should be considered as an optional emergency procedure following external fixation in patients who remain haemodynamically unstable and are considered too sick to leave the operating table and be exposed to the delay required for transfer and initiation of an angiographic procedure or as an added step whenever intraperitoneal exploration was necessary. Packing should obviously be considered if angiography is not available. Packing is more efficient against low-pressure than it is against high-pressure bleeding. In a series of 18 pelvic disruptions with unstable haemodynamical condition requiring pelvic packing, Totterman subsequently performed angiographic imaging in all 18 and found that 80% of these still presented with active arterial bleeding despite the presence of the retroperitoneal packing [26]. In a classic publication, using latex injection in deceased pelvic trauma victims, Huttinnen and Slatis had found arterial injuries in only 15% [11]. More recent clinical series report higher rates. Multiple simultaneous arterial bleeding were found in 75% of a series of 35 pelvic ring fractures requiring angiography [27], with the bleeding sources depending upon the location and degree of skeletal instability. Interestingly, in the same study, bleeding sources at the posterior pelvis (superior gluteal, internal iliac) were less common than anterior bleeding sources (pubendal artery). The same observation was made in our present series, where in 16 patients (27%) requiring angiography, the bleeding was more common at the level of the anterior pelvic ring than in the gluteal or sacral branches (Box 1).

In our institution, angiography is performed in the angiographic suite, a short distance away from the operating room. Patients can be transferred, if required, while maintaining general anaesthesia from the operating room to the angiography suite. This will occur as soon as the abdomen has been cleared as a source of bleeding or if hypotension persists. No complications, such as gluteal muscle necrosis, were observed in our patients following selective embolization. Aortic clamp or intraaortic balloon may be used too as salvage procedure (one case of aortic balloon in our series who died day 2) [28].

With a qualified team of interventional radiologists available, we found that the sequence of skeletal fixation followed by angiographic embolization is the best procedure, without exposing our patients to unnecessary invasive surgical procedures or added surgical incisions which would compromise future ORIF, or require staged second look procedures such as needed for removal of preperitoneal packing. The average ISS score of our four groups are different and show a significant increase between groups 1 (ISS = 49) and 4 (ISS = 59). This obviously represents a strong limiting factor as to the conclusions that may be extracted from our database. The high ISS score (59) of patients in group 4 reflects the severity of their condition (Table 2) and may explain the, perhaps precipitous and desperate attempts of extreme life-saving invasive surgical procedures undertaken in these patients, who were dying of massive bleeding. Our findings do however support the concept of a step-by-step algorithm involving external fixation an angiography as the best choice. We want especially to prevent crash-laparotomy before any other procedures (Fig. 2). In this series, all survivors underwent definitive ORIF as soon as their general condition allowed. Pelvic ring lesions were stabilized using plates and screws with an average delay of 3.5
Unstable pelvic ring injury with hemodynamic instability: What seems the best procedure choice and sequence in the initial management?


Table 2 Characteristics of patients from group 4 with high degree of severity condition.

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Laparotomy</th>
<th>Packing</th>
<th>Arteriography</th>
<th>Pelvic</th>
<th>Head</th>
<th>Chest</th>
<th>Abdomen</th>
<th>Type pelvic fracture</th>
<th>Limbs</th>
<th>Soft tissue</th>
<th>ISS</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LJ</td>
<td>52</td>
<td>f</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>Sacro-iliac</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>Vein azygos</td>
</tr>
<tr>
<td>LD</td>
<td>16</td>
<td>h</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>C</td>
<td>0</td>
<td>0</td>
<td>75</td>
<td>Hemorrhagic abdomen</td>
</tr>
<tr>
<td>RF</td>
<td>23</td>
<td>f</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>57</td>
<td>Chest ++</td>
</tr>
<tr>
<td>GD</td>
<td>16</td>
<td>h</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>C</td>
<td>0</td>
<td>0</td>
<td>75</td>
<td>Hemorrhagic abdomen</td>
</tr>
<tr>
<td>EH</td>
<td>38</td>
<td>h</td>
<td>Thoraco</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>Transv, SI</td>
<td>0</td>
<td>0</td>
<td>51</td>
<td>Iliac arteriography</td>
</tr>
<tr>
<td>MP</td>
<td>64</td>
<td>h</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>SI</td>
<td>+</td>
<td>0</td>
<td>57</td>
<td>Sub-clavian arteriography</td>
</tr>
<tr>
<td>AL</td>
<td>39</td>
<td>f</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>54</td>
<td>Liver</td>
</tr>
</tbody>
</table>

Mean ISS = 59 range (50–75).
days post-injury for symphysis fixation, 5 days for posterior ring fixation, and 8 days post-injury for acetabulum resection and fixation. No infections linked to the temporary use of the external fixators, anterior frames or C-clamps, were observed in our series.

Conclusion

The management of haemorrhagic instability linked to pelvic ring disruptions involves a sequence of therapeutic events, which is more important than the events themselves.

Despite the limitations regarding the diverging ISS values between our four groups of patients, we believe that our data strongly supports, the initial application of an external fixator, especially prior to laparotomy, or packing. Angiographic embolization is the method of choice whenever haemodynamic instability coexists with an unstable pelvic disruption. Immediate laparotomy, without preliminary fixation, does not allow for the control of bleeding and seems to lead to an high rate of intraoperative mortality. Retroperitoneal exploration should be avoided. If patients remain hemodynamically unstable after application of an external fixator, we believe that angiography is the next procedure to consider. If angiography is not available within a reasonable time-frame, packing remains an invasive salvage treatment.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


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