Incidence of chronic pain six years after major trauma.

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Title:

Incidence of chronic pain six years after major trauma.

Authors:

Knut Magne Kolstadbraaten[1]

Ulrich Johannes Spreng[2]

Kristin Wisloeff-Aase[2,3]

Christine Gaarder[1]

Paal Aksel Naess[1,3]

Johan Raeder[2,3]

[1]Department of Traumatology, Oslo University Hospital

[2]Department of Anaesthesiology, Oslo University Hospital

[3]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo

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Correspondence: Johan Ræder, Dept. of Anaesthesiology, Oslo University Hospital, Pb 4950 Nydalen, 0242 Oslo, Norway

Telephone +4792249669, faxnr: +4722119857, email: johan.rader@medisin.uio.no

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Abstract

Background: The initial treatment of major trauma focuses on life saving measures.

In surviving patients, chronic pain may be a serious problem, but the long term incidence and potential risk factors are not very well studied.

Methods: All adult trauma patients included in the institutional trauma registry in 2007 were assessed for eligibility. Exclusion criteria were: Injury Severity Score (ISS) < 9, endotracheal intubation before or during admission, spinal cord lesion, known chronic drug or substance abuse, major surgery within three hours after admission. A patient questionnaire was sent out six years after injury focusing on frequency and intensity of pain. A subgroup analysis was done in patients with thoracic injuries, comparing patients with and without epidural analgesia (EDA).

Results: 68 patients were included in the study. 69 % reported pain six years after injury and 24 % had severe pain. The severity of the injury was a risk factor for development of chronic pain, whereas pain during initial hospital stay was not. In patients with thoracic injuries there was no correlation between initial treatment with epidural analgesia and decreased incidence of chronic pain, however patient numbers were small. Opioids were the main analgesics used initially; no patients received NSAIDs or peripheral nerve blocks during the first 24 hrs.

Conclusion: Two thirds of the trauma patients had chronic pain six years after injury and one out of four had severe pain. The initial pain treatment was focused on opioids.~~ and not adequate.~~

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Introduction:

The initial treatment of major trauma, both pre- and in-hospital, focuses on life saving measures. Concomitant pain is usually treated with opioids upon patient request (1, 2), without structured protocols for preventive, modern multimodal analgesia (2). In patients who survive major trauma, chronic pain may be a significant problem in the years to come (3-5), requiring long-term follow-up (3). Prolonged opioid pain-treatment in these patients may result in opioid abuse and major secondary health problems (6). Chronic pain can occur after the peripheral and central pain receptors are being sensitized in the acute phase due to release of inflammatory mediators (7, 8). Although there is a strong association between the severity of initial, post-operative pain and the incidence of chronic pain (8), controversy exists on whether optimal prophylaxis and treatment of acute pain may result in reduced incidence of chronic pain, and whether some modalities of treatment are better than others in this aspect (7, 8). For instance, the use of loco-regional blocks, such as epidural analgesia (EDA), has shown promising results in reducing the number of patients developing chronic pain in the post-surgical setting (9).

The primary aim of this study was to determine the incidence and severity of chronic pain six years after moderate to severe trauma (i.e. Injury Severity Score (ISS) ≥ 9) in non-intubated patients who were primarily admitted to Oslo University Hospital, Ullevaal, the largest trauma centre in Norway with a catchment area of 2.8 million people.

The secondary aims were to explore associations between chronic pain and strength of initial pain, as well as type and quality of pain treatment given during the admission period, and initial hospital stay.

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Methods

The study was reviewed and approved by the Regional Committee for Medical Research Ethics of South-Eastern Norway (Ethical Committee No. 2011/169) and informed patient consent was obtained for an observational, follow-up study design in adult patients.

All trauma patients included in the institutional trauma registry in 2007 were assessed for eligibility. Exclusion criteria for the study were: Injury Severity Score (ISS) < 9, age less than 18 years or more than 80 years, transfer from other hospitals, endotracheal intubation before admission or in the emergency department (ED), spinal cord lesion, known chronic drug or substance abuse, major surgery within three hours after admission or discharge from hospital within 6 hours.

The following data were extracted from the institutional trauma registry; age, gender, Abbreviated Injury Scale (AIS), ISS, New Injury Severity Score (NISS), mechanism of injury, time of injury, time of admission, time spent in the ED, time spent in the Intensive Care Unit (ICU) and total length of stay in hospital.

From the patients charts the following data were extracted: analgesics given during the first 24 hours in hospital, pain scores (if applicable, i.e. Visual Analogue Scale (VAS) or Verbal Numeric Rating Scale (VNRS)), and use of regional blocks, including EDA.

In a subset of patients with moderate to severe thoracic trauma (i.e. more than two rib fractures), the use or non-use of EDA was registered.

About six years post injury, patients who were alive and had a postal address in Norway, received a written questionnaire with a prepaid stamped envelope to return to the principal investigator. A reminder was sent to patients not responding within one month.

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The questionnaire (see Amendment 1) was designed to assess recall of initial hospital stay pain (-5 point Likert scale: none-weak-medium-strong-very strong) and whether the respondent still had any pain related to the trauma. In case of persisting pain, further questions had to be answered related to frequency (i.e. daily, more than once a week, more than once a month, once a month or less) and intensity of pain (weak, medium, strong, very strong).

Chronic pain was defined as any pain which could be attributed to the injury six years earlier. Severe chronic pain was defined as either: medium pain daily or more, strong pain weekly, or any case of very strong pain last month.

All data were entered in SPSS (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, USA) as frequency tables and reported as mean, standard deviation and range as appropriate. A multiple logistic regression analysis was constructed to assess the impact of age, gender, ISS and the amount of fentanyl given in the emergency room, on the frequency of chronic pain.

The association between initial hospital pain was tested against chronic pain/no chronic pain with Chi-square test (2x5 tables). A further analysis was performed on the subgroup of patients with thoracic injuries with non-randomized use of EDA as an extra independent variable in the logistic regression analysis.

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Results:

A total of 125 patients were eligible from the inclusion and exclusion criteria. (Fig 1, consort flow chart). Out of these 125 patients, 27 patients were unavailable to follow up (dead or living abroad), the questionnaire was sent to 98 patients, and returned by 68 (69%, Fig 1), which are reported here. The mechanism of injury was blunt in all patients. Road traffic accidents were the cause in 69%, whereas 25 % were injured as a results of falls.

Data on age, ISS, time used, and drugs administered in the ED are listed in table 1. Opioids, ketamine and diazepam were used, whereas no patient received non-steroidal anti-inflammatory drugs (NSAIDs), peripheral nerve blocks or EDA during the short stay (on average 29 min) in the emergency room. Apart from EDA no other type of regional block or nerve-blocks was performed during the subsequent first 24 hours after trauma in the patients. Systematic pain registration (VAS or VNRS) was not recorded in any patient in the ED, and only in 22% of the patients during the next 24 hours.

In the 68 returned questionnaires, a total of 47 (69%) patients reported chronic pain related to the injury and in 25 (37%) the occurrence was at least once per week (table 2).

The intensity of worst pain was described as strong or very strong in 13 (19%) of the patients. Among the 16 patients (24%) suffering from pain which was classified as severe chronic pain (table 2), the intensity of initial pain varied considerably, as did length of stay in the ICU and total LOS in hospital. Four cases with severe chronic pain were admitted for injuries with no need of overnight observation in hospital, whereas five of the more severely injured patients (defined as an ISS > 15) did not report chronic pain. ISS was the only variable with significant correlation to chronic pain (p=0.03) in the multivariate analyses.

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The initial pain during the first days in hospital was recalled to be “strong” or “very strong” in 62% of the patients, and during the rest of the hospital stay in 47% of the patients (table 3).

There was no significant difference between patients with chronic pain versus no chronic pain in frequency or strength of recalled pain from any part of the initial hospital period after the trauma (Chi-square test, p=0.4-0.6) (table 3).

A total of 72% (26/36) of the patients in the subgroup with moderate to severe thoracic trauma reported chronic chest pain, which was not different from the incidence in the total study population. Eleven of the 36 (31%) patients with thoracic injury received EDA during the first 24 hours. The reported frequency of chronic pain was not significantly different in the group of patients in whom EDA was administered (12 patients, 83 % with chronic pain) compared with the group without EDA (24 patients, 67 % with chronic pain).

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Discussion

In this study of major trauma patients, 69% of the patients reported chronic pain six years after the injury and 24 % reported severe chronic pain. The severity of trauma, as defined by the ISS, was the only studied factor significantly associated with the frequency of chronic pain. There was a high incidence of recall of strong or very strong pain during the initial hospital stay, but with no correlation to later chronic pain. Almost no systematic pain documentation was used in our hospital at the time of the injuries, and apart from the cases of epidural analgesia, opioids were the most frequent analgesic in use.

The incidence of severe chronic pain post injury varies in the literature. The frequency of 69 % reporting chronic pain in our study is a high number. In a study involving patients with moderate injury (in which mean ISS was 12), 15% of the patients experienced chronic pain 12 months post injury (4). A second study reported that 63% of patients had trauma related pain 12 months after injury (5).

One possible explanation for the high percentage of patients with chronic pain in our study may be that we only included patients with moderate or severe injury (ISS ≥ 9) and severity of trauma was independently associated with the frequency of chronic pain. This observation is in accordance with the findings in a study by Holmes et al. who reported chronic pain to be associated with the abbreviated injury scale AIS score (4). They also described three additional aspects which were predictive of the occurrence of chronic pain 12 months post injury: to be unemployed before the injury, to have any pain before the injury, and to have a catastrophizing attitude in general (4). Rivera et al demonstrated the following risk factors for developing chronic pain 12 months after major trauma: female gender, untreated depression before the accident, low educational level and physical limitations before the accident (5).

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In our study ISS was the only independent factor found to be significantly associated with chronic pain incidence; whereas age, gender, pre-trauma pain, pre-trauma analgesic use, as well as different aspects of the primary pain and trauma care were not.

Our finding that initial pain after trauma was treated mostly with opioids, is consistent with other studies (1, 10). Although opioids are effective analgesics in a dose related manner in trauma patients, they are associated with several adverse side effects, such as respiratory depression and nausea (10). Also, the use of opioids has been demonstrated to facilitate the development of hyperalgesia, which in turn is associated with increased risk of chronic pain. (8, 9). Although 31 of our patients (46%) had extremity injuries, none of these patients were treated with peripheral nerve blocks during the first 24 hours.

Strong initial pain after surgical trauma has been reported to be strongly associated with high incidence of chronic pain (7). However, it is still disputed if there is a causal relationship, or merely a coincidence of strong initial pain and chronic due to type or magnitude of trauma (11). In our study of non-surgical trauma, about 50% of the patients (62% during first days, 47% during rest of the stay) reported strong or very strong pain during the hospital stay, but we found no association with the incidence of chronic pain, suggesting that initial pain does not seem to be a major player in the development of chronic pain.

Several authors have concluded that regional analgesia is suitable for trauma patients (12-14). Regional analgesia can relieve strong pain from a limited, defined area of the body without the systemic drug influence from opioid drugs.

Thoracic EDA is a suitable technique for pain treatment of sternal and/or multiple rib fractures and can be performed both in the ED and the ICU (12, 15, 16). Epidural analgesia has been found to reduce the incidence of chronic pain after thoracic surgery (17). Still, while the short-term and beneficial effects of EDA in this setting are well studied (12, 15), there are little data on the effect of EDA on preventing chronic pain in patients with traumatic chest wall injuries. We found no correlation between the use of epidural analgesia and chronic pain in our subgroup of patients with thoracic injury.

The strengths of our study include the strict exclusion/inclusion criteria and the access to reliable initial trauma data after 6 years, from our trauma registry. We wanted to include only non-intubated patients as patients with intubation are given general anaesthesia and deep sedation, usually for many days, which affects the ability to register and remember pain. We also focused on patients with moderate and severe injuries and excluded patients who underwent surgery within three hours after admission, in order to focus on pain due to the trauma per se. The long observation period of six years eliminated cases of prolonged transient pain and left us with the data on chronic pain beyond the first years.

The limitations of our study include its retrospective design, and the relatively limited number of patients. Furthermore, the questionnaire did not include data on psycho-social aspects, which is known to be correlated with incidence of chronic pain after surgical trauma (4). Also, the questionnaire was aimed to be made short and simple, with verbal 5 point Likert scales for pain recall. There were no options for patients to expand on details of their pain and no questions on neuropathic pain, everyday function or present quality of life. The treatment of patients with major thoracic injuries in 2007 was not based on randomization or strict criteria for the use of EDA, and it is likely that there was a selection bias, i.e. patients with stronger pain/more severe injury were more likely to receive EDA. Also, many patients were not eligible for epidural injection, either because of the use of anticoagulants, haemodynamic instability or the nature of other injuries.

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In conclusion, more than two thirds of moderately to severely injured, conscious patients had chronic pain six years post injury. One out of four patients reported severe chronic pain.

The severity of the injury was a risk factor for development of chronic pain, whereas no association between initial pain in hospital and chronic pain was demonstrated.

Based on these results, randomized control trials are warranted in trauma patients, to evaluate the effects of ~~more~~ optimal initial pain documentation and treatment, as well as other measures with the potential aim of reducing the high incidence of chronic pain.

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References

1. Curtis KM, Henriques HF, Fanciullo G, Reynolds CM, Suber F. A fentanyl-based pain management protocol provides early analgesia for adult trauma patients. J Trauma. 2007;63(4):819-26.

2. American College of Surgeons Committee on T. Advanced trauma life support : ATLS : student course manual. 9th ed. ed. Chicago, Ill: American College of Surgeons; 2012.

3. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10(4):287-333.

4. Holmes A, Williamson O, Hogg M, Arnold C, Prosser A, Clements J, et al. Predictors of pain 12 months after serious injury. Pain Med. 2010;11(11):1599-611.

5. Rivara FP, Mackenzie EJ, Jurkovich GJ, Nathens AB, Wang J, Scharfstein DO. Prevalence of pain in patients 1 year after major trauma. Arch Surg. 2008;143(3):282-7.

6. Chacko J, Greenstein J, Ardolic B, Berwald N. Effect of an emergency department opioid prescription policy on prescribing patterns. The American journal of emergency medicine. 2017;35(9):1327-9.

7. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618-25.

8. Lavand'homme P. The progression from acute to chronic pain. Curr Opin Anaesthesiol. 2011;24(5):545-50.

9. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis†. British Journal of Anaesthesia. 2013;111(5):711-20.

10. Malchow RJ, Black IH. The evolution of pain management in the critically ill trauma patient: Emerging concepts from the global war on terrorism. Crit Care Med. 2008;36(7 Suppl):S346-57.

11. Badiola IJ. Can Chronic Pain Be Prevented? Anesthesiol Clin. 2016;34(2):303-15.

12. Choi JJ, Lin E, Gadsden J. Regional anesthesia for trauma outside the operating theatre. Curr Opin Anaesthesiol. 2013;26(4):495-500.

13. De Buck F, Devroe S, Missant C, Van de Velde M. Regional anesthesia outside the operating room: indications and techniques. Curr Opin Anaesthesiol. 2012;25(4):501-7.

14. Gregoretti C, Decaroli D, Miletto A, Mistretta A, Cusimano R, Ranieri VM. Regional anesthesia in trauma patients. Anesthesiol Clin. 2007;25(1):99-116.

15. Bulger EM, Arneson MA, Mock CN, Jurkovich GJ. Rib fractures in the elderly. J Trauma. 2000;48(6):1040-6.

16. Winters BA. Older adults with traumatic rib fractures: an evidence-based approach to their care. J Trauma Nurs. 2009;16(2):93-7.

17. Tiippana E, Nilsson E, Kalso E. Post-thoracotomy pain after thoracic epidural analgesia: a prospective follow-up study. Acta Anaesthesiol Scand. 2003;47(4):433-8.

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Table 1

Patient characteristics (n=68), analgesics and sedatives administered in the ED (Emergency Department)

	Mean ± SD (range)
Age, yrs	43 ± 17 (18-77)
ISS	18 ± 8 (10-50)
Time spent in ED (min)	28 ± 12 (14-76)
Analgesics administered in ED (mean values in patients (n) given the drug)	
Fentanyl (µg) (n=55)	131 ± 66 (50-400)
Alfentanil (mg) (n=4)	0.5 ± 0.2 (0.25-0.75)
Ketamine (mg) (n=6)	52 ± 39 (15-100)
Sedatives administered in the ED	
Diazepam (mg) n=24	3.7 ± (1.25-10)

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Table 2

Frequency of pain related to the injury 6 years earlier (n=68)

	No pain	Weak	Medium	Strong	Very strong
No Pain	21	0	0	0	0
< 1 per month	0	5	5	0	0
More than once a month	0	2	7	3	0
More than once a week	0	1	8	2	0
Daily	0	0	6	6	2
Total	21	8	26	11	2

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Table 3:
Recall of pain associated with the trauma and initial hospital stay – 6 years after major trauma

Recall of Pain from:	None (n)	%	Weak (n)	%	Medium (n)	%	Strong (n)	%	Very strong (n)	%	Do not remember (n)	%	Total
- Injury site	4	5.9	2	2.9	8	12	10	15	27	40	17	25	68
- During transport	8	12	5	7.4	7	10	6	8.8	13	19	29	43	68
- During first hours in hospital	8	12	8	12	8	12	6	8.8	13	19	25	37	68
- During first days in hospital	4	5.9	3	4.4	9	13	21	31	21	31	10	15	68
- During rest of the stay in hospital	3	4.4	6	8.8	19	28	22	32	10	15	7	10	67*
- Pain after discharge	3	4.4	8	12	17	25	24	35	15	22	1	1,5	68

*1 missing

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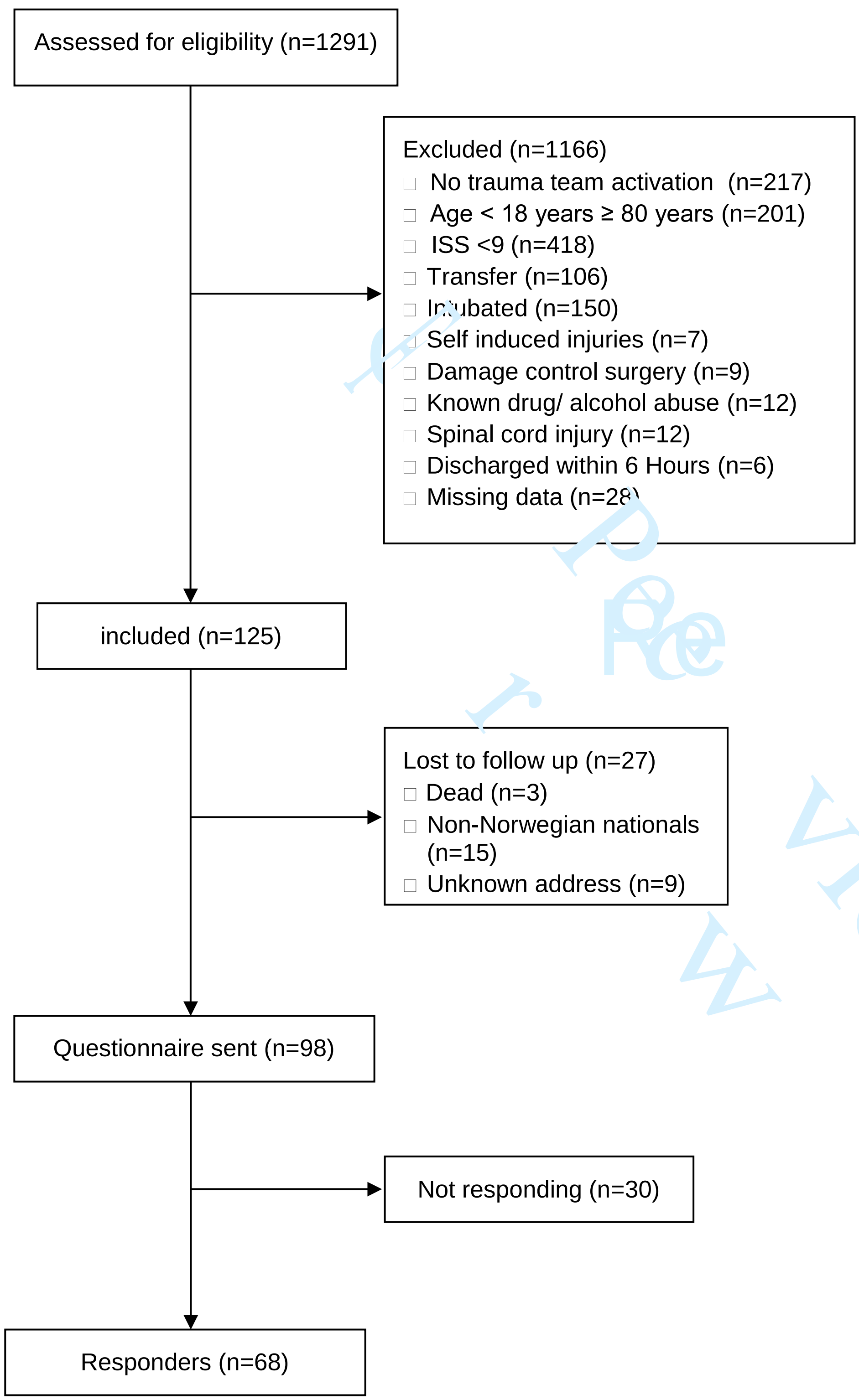

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We would like to ask you some questions about pain intensity and the duration of pain after injury. We kindly ask you to tick off the right box for your answer. We know it is a long time since the injury and if you do not remember please tick off «Do not remember". You are welcome to add comments on the last page when you have finished the questionnaire.

Questionnaire – Part A – Information about the pain after the injury:

1) Did you have pain on scene?
- ☐ No
- ☐ Weak
- ☐ Medium
- ☐ Strong
- ☐ Very Strong
- ☐ Do not remember

2) Did you have pain during the transportation to the hospital?
- ☐ No
- ☐ Weak
- ☐ Medium
- ☐ Strong
- ☐ Very Strong
- ☐ Do not remember

3) Did you have pain in the first hours after admission to the hospital?
- ☐ No
- ☐ Weak
- ☐ Medium
- ☐ Strong
- ☐ Very Strong
- ☐ Do not remember

4) Did you have pain in the first days after admission to the hospital?
- ☐ No
- ☐ Weak
- ☐ Medium
- ☐ Strong
- ☐ Very Strong
- ☐ Do not remember

5) Did you have any further pain during your hospital stay?
- ☐ No
- ☐ Weak
- ☐ Medium
- ☐ Strong
- ☐ Very Strong
- ☐ Do not remember

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6) Did you have pain after discharge from the hospital?
☐ No
☐ Weak
☐ Medium
☐ Strong
☐ Very Strong
☐ Do not remember

7) For how long did you have daily pain

____________(Please specify the duration of pain in days, months, years or still daily pain)

Part B – Information about present pain:

1) Do you still have pain related to the injury some years ago?
☐ No, I never feel pain related to the injury. If this is your answer, you do not answer the rest of the questions.
☐ Yes, if this is your answer, please answer the following questions:

2) How often do you feel such a pain?
☐ Daily
☐ Weekly
☐ Monthly
☐ Less than once a month

3) How would you describe the maximum intensity of the pain?
☐ Weak
☐ Medium
☐ Strong
☐ Very strong

☐ Yes, I accept to be contacted by a phone call for additional questions about the pain.

My phone number is:__________________

☐ No, I do not want to be contacted by a phone call.

We will thank you for your time and your valuable information and sharing your information with us.

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