Original Article

Systemic Inflammatory Response Syndrome (SIRS) in Serious Chest Injuries: Is a Pharmacological Blockade Effective?

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Purpose: There has been an ongoing increase in the frequency and severity of blunt chest injuries. Their rather high lethality is caused by the injury alone as well as by the following systemic inflammatory response. The aim of the study is to verify the efficacy of the pharmacological blockade of the systemic inflammatory response syndrome (SIRS) in serious blunt chest injuries, and to identify whether the administration of indomethacin as a cyclooxygenase inhibitor could prevent a multiorgan dysfunction (MODS) and a multiorgan failure (MOF).
Methods: Patients were divided into 4 Groups according to trauma severity — injury severity score (ISS) and into two subgroups — an indomethacin subgroup where patients received indomethacin together with standard therapy, and a non-indomethacin subgroup.
Results: Eighty-four patients were included in the study and 33 patients were given indomethacin. In Groups III and IV there was a later increase in inflammatory markers in patients treated with indomethacin. The elevation of inflammatory markers and the period of mechanical ventilation support in patients treated with indomethacin were shorter in Groups II and III. Seven (8.3%) patients died. Six of the seven dead patients were from the non-indomethacin subgroup. MOF was the cause of death in two patients in the non-indomethacin subgroup and in one patient in the indomethacin subgroup.
Conclusion: The results obtained during the first 20 months of the study imply that a certain number of patients with serious blunt chest trauma could benefit from indomethacin administration. (Ann Thorac Cardiovasc Surg 2005; 11: 232–7)

Key words: blunt chest trauma - SIRS - MOF - indomethacin

Introduction

There has been an ongoing increase in the frequency and severity of chest injuries in the previous years. Serious blunt chest injuries are accompanied with the worsening of ventilation mechanics due to the chest and lungs injuries as well as with a systemic inflammatory response syndrome (SIRS) that always affects the lungs function. Therefore, the development of an injury-induced respiratory failure is multifactorial and timely pharmacological intervention is a suitable addition to the treatment, thus improving prognosis in some patients with a serious chest trauma.

The objective of this study is to verify the efficacy of the pharmacological blockade of SIRS in serious blunt chest injuries, and to identify whether the administration of indomethacin as a cyclooxygenase inhibitor could prevent multiorgan dysfunction (MODS) and multiorgan failure (MOF). This clinical study should imply whether this therapeutic approach results in lower morbidity and lethality.

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Table 1. Frequency of particular types of thoracic injuries in ISS Groups

	I	II	III	IV
Rib fractures up to 4	20	21	8	5
Rib fractures more than 4	6	9	4	4
Pulmonary contusion	4	15	17	11
Partial pneumothorax	12	11	5	0
Total pneumothorax	7	7	5	4
Haemothorax	13	19	10	9
Pneumomediastinum	2	3	2	0
Flail chest	2	2	1	0
Bronchus perforation	0	1	0	0
Diaphragmatic rupture	0	0	1	0
Heart contusion	0	1	1	0

Methods

Approvals from the Institute of Medical Studies Review Board as well as from the Ethical Committee were obtained. Every patient signed an informed consent form before being enrolled in the study.

Indomethacin is a highly effective inhibitor of the synthesis of prostaglandins, which plays the crucial role in SIRS development.

Patients were divided in four Groups, depending on the extent of the injury severity score (ISS).[7)]
Group I included patients with an ISS of up to 17 where the development of SIRS is not expected. Group II comprised patients with an ISS ranging from 18 to 30 where subsequent SIRS may lead to the dysfunction or to the failure of the other organs and systems that were not affected by proper injury. Group III involved patients with an ISS ranging from 31 to 40 (severe trauma). Group IV contained critically injured patients with ISS of 41 and higher.

The following parameters are monitored in the patients: mechanical ventilation support; i.e. the type and the total time of ventilation, blood gases, the SIRS score,[9)] free oxygen radicals, total antioxidant status (mmol/l), PINI index — prognostic inflammatory nutritional index/CRP (mg/l), albumin (g/l), prealbumin (g/l), orosomucoid (g/l)/, lactate (mmol/l), the C3 and C4 components of a complement (g/l), pulmonary X-ray or CT, and total lethality.[15)]

In view of that fact that the probability distribution of monitored statistical characters is not known, we had to evaluate the taken values by means of non-parametric tests.

Considering the available data, the Wilcoxon two-sample test appears the most appropriate method to verify the hypothesis that indomethacin affects the monitored characters. In all cases, we formulated the null hypothesis as H0: indomethacin does not affect a monitored character. Testing criterion U was applied in the form of U=min{U1, U2}, where

Table 2. Randomization of patients into indomethacin and non-indomethacin subgroups

	I	II	III	IV
Indomethacin	11	12	8	2
Non-indomethacin	20	16	7	8
Total	31	28	15	10

$$U_1 = mn + \frac{m(m+1)}{2} - T_1 \quad U_2 = mn + \frac{n(n+1)}{2} - T_2$$

T1 and T2 are the summations of the order of the values of the first and second samplings during a combined sampling organized according to a size; m and n area the ranges of samplings. The null hypothesis is rejected in the event that the following applies to the value of the testing criterion: U≤w (α), where w (α) is a critical limit and α is the level of test significance. The testing was completed at two commonest levels of significance: α=0.01 and α=0.05. Even though non-parametric tests can be applied to the smaller ranges of random samplings, the minimal lower limit of the number of data must be complied with. This is why certain Groups of patients could not be evaluated.

Results

Eighty-four consecutive patients with thoracic injuries admitted to the ICU of the Department of Surgery of the Institute of Medicine, Pardubice Hospital, between February 2002 and November 2003 were evaluated. A traffic accident was the cause of injury in 55 (65.5%) cases, a fall from a height in 20 (23.8%) cases, and 9 (10.7%) cases were due to other mechanisms. Patients were divided into four Groups, depending on the extent of trauma severity.[7)] Patients in each Group were randomized into two subgroups, an indomethacin subgroup and a non-indomethacin subgroup. In the indomethacin subgroup, the patients, received — except their standard therapy — indomethacin per rectum (®Berlin-Chemie) in two 100 mg doses a day.

The frequency of the particular types of thoracic injuries in ISS Groups is shown in Table 1.

The randomization of patients into the indomethacin

Table 3. Frequency of particular types of interventions in ISS Groups

	I	II	III	IV
Mechanical ventilation	1	6	10	7
Chest tube	9	7	7	6
Videothoracoscopy	1	0	0	0
Thoracotomy	0	1	1	1
Thoracic puncture	2	3	1	0

Table 4. Number of patients with artificial pulmonary ventilation/duration of artificial pulmonary ventilation

	I	II	III	IV
Indomethacin	1/0	3/5.3	5/10.0	2/12
Non-indomethacin	0/0	3/8.7	5/15.2	5/9.8
Total	1	6	10	7

Table 5. Lethality in particular subgroups

	I	II	III	IV
Indomethacin	0	0	1	0
Non-indomethacin	0	1	1	4

and non-indomethacin subgroups in ISS Groups shows Table 2.

The necessity of surgical or other intervention in the individual Groups is shown in Table 3. Table 4 displays the application and duration of mechanical ventilation support. The non-indomethacin subgroup in Groups II and III showed a markedly longer time of mechanical ventilation support. In Group IV comprising critically injured patients, the subgroup of patients with indomethacin administration required a somewhat longer time of mechanical ventilation support (12.0/9.8 days). This was influenced by the early death of three patients in the non-indomethacin subgroup who thus could not be ventilated or hospitalized.

Considering the number of data, only one Group, i.e. Group III, could be evaluated. The value of testing criterion U=7. The critical limits were: w (0.01)=0 and w (0.05)=2. Conclusion: Because it holds true that U>w (α), we do not reject the null hypothesis, and the time of ventilation is not affected by the administration of indomethacin.

Of all the patients included in our study seven (8.7%) died during the period in concern. Six of them belonged to the non-indomethacin subgroup. Cerebral contusion was the reason of death in four cases, which means that thoracic injuries were only accessory. MOF was the cause of death in two patients in the non-indomethacin subgroup and in one patient in the indomethacin subgroup. This is obvious from Table 5.

Table 6 shows the time of SIRS onset and duration according to the individual subgroups. Considering the number of data, only Groups II and III could be evaluated.

Onset. Group II: The value of testing criterion U=40. The critical limits were w (0.01)=12 and w (0.05)=18. Conclusion: Because U>w (α), we do not reject the null hypothesis; the time of the onset of SIRS is not affected by the administration of indomethacin.

Group III: The value of testing criterion U=15. The critical limits were w (0.01)=1 and w (0.05)=5. Conclusion: Because U>w (α), we do not reject the null hypothesis; the time of the onset of SIRS is not affected by the administration of indomethacin.

Duration. Group II: The value of testing criterion U=19.5. The critical limits were w (0.01)=10 and w (0.05)=16. Conclusion: Because U>w (α), we do not reject the null hypothesis; the time of the duration of SIRS is not affected by the administration of indomethacin. In this case, however, the value of the testing criterion is close to a critical limit at a significance level of 0.05, thus resulting in a realistic assumption that once the data are complete the hypothesis could be rejected and the effect of indomethacin could then be proven.

Group III: The value of testing criterion U=8.5. The critical limits were w (0.01)=1 and w (0.05)=5. Conclusion: Because U>w (α), we do not reject the null hypothesis; the time of the duration of SIRS is not affected by the administration of indomethacin. It is also probable in this case that once the data are complete the test result could confirm the influence of the administration of indomethacin over the duration of SIRS.

Table 7 demonstrates the first increase in the levels of

Table 6. Onset of SIRS (in days)/duration of SIRS (in days)

	I	II	III	IV
Indomethacin	0.5/1.5 (7 sine)	1.6/1.4 (5 sine)	0.4/5.8 (3 sine)	0/5.5
Non-indomethacin	0.3/4.1 (11 sine)	0.4/4.1 (4 sine)	2.0/10.0	0.5/5.3

Table 7. The first increase of inflammatory markers (in days)/duration of increase of inflammatory markers (in days)

	I	II	III	IV
Indomethacin	1.3/2.0 (5 sine)	1.3/2.8 (4 sine)	2.3/7.7 (1 sine)	2.5/8.5
Non-indomethacin	1.8/1.0 (15 sine)	2.8/5.1 (7 sine)	1.0/8.7	1.3/5.1

inflammatory markers and the duration of such high levels. The non-indomethacin subgroup of Group I comprised twenty patients. Eleven of them did not display any signs of SIRS, the others did, on an average, after 0.3 of the day and the signs lasted for an average period of 4.1 days. An increase in the levels of inflammatory markers in this subgroup took place after an average of 1.8 days and lasted for an average period of 1.0 day. Fifteen patients in this subgroup did not demonstrate any increase in inflammatory markers. The indomethacin subgroup of Group I comprised eleven patients. Seven patients had no signs of SIRS, the others developed the SIRS signs after an average period of 0.5 day and displayed those signs for 1.5 days. An increase in inflammatory markers occurred after 1.3 days and lasted for an average period of 2.0 days. Five patients in this subgroup did not experience any increase in inflammatory markers. By analogy, the situation in Groups II, III and IV is displayed in Tables 6 and 7.

Considering the number of data, only Groups I, II and III could be evaluated in statistical terms.

The first increase in the levels of inflammatory markers. Group I: The value of testing criterion U=9. The critical limits were w (0.01)=1 and w (0.05)=3. Conclusion: Because U>w (α), we do not reject the null hypothesis; the first increase in inflammatory markers is not affected by the administration of indomethacin. Group II: The value of testing criterion U=29.5. The critical limits were w (0.01)=11 and w (0.05)=15. Conclusion: Because U>w (α), we do not reject the null hypothesis; the first increase in inflammatory markers is not affected by the administration of indomethacin. Group III: The value of testing criterion U=19. The critical limits were w (0.01)=4 and w (0.05)=8. Conclusion: Because U>w (α), we do not reject the null hypothesis; the duration of the increase is not affected by the administration of indomethacin.

The duration of high levels of inflammatory markers. Group I: The value of testing criterion U=7.5. The critical limits were w (0.01)=1 and w (0.05)=3. Conclusion: Because U>w (α), we do not reject the null hypothesis; the duration of the increase is not affected by the administration of indomethacin. Group II: The value of testing criterion U=25.5. The critical limits were w (0.01)=9 and w (0.05)=15.

Conclusion: Because U>w (α), we do not reject the null hypothesis; the duration of the increase is not affected by the administration of indomethacin. Group III: The value of testing criterion U=17. The critical limits were w (0.01)=4 and w (0.05)=8. Conclusion: Because U>w (α), we do not reject the null hypothesis; the duration of the increase is not affected by the administration of indomethacin.

Table 8. Average duration of hospital stay (in days)

	I	II	III	IV
Indomethacin	12.1	12.7	26.4	29.0
Non-indomethacin	12.0	20.0	23.4	26.3

The average time of hospital stay is comparable to Group I. The hospital stay is markedly shorter in the indomethacin subgroup of Group II (12.7/20.0 days), difference: 7.3 days (Table 8).

Considering the number of data, only Groups I, II and III could be evaluated.

Group I: The value of testing criterion U=88.5. The critical limits were w (0.01)=48 and w (0.05)=62.

Conclusion: Because U>w (α), we do not reject the null hypothesis; the duration of hospitalization is not affected by the administration of indomethacin. A sufficient number of values were identified in this Group; therefore, we tested the same hypothesis also with the aid of the following testing criterion

$$U = \frac{\left|U_1 - 0.5mn\right|}{\sqrt{\frac{mn}{12}(m+n+1)}}$$

that displays asymptotically normal probability distribution when the hypothesis applies. We reject the hypothesis when it holds true that the value of testing criterion U≥z (α), where z (α) is the critical limit of normal distribution. The value of testing criterion U=0.8877. The critical limits were z (0.01)=2.58 and z (005)=1.96. Conclusion: This test also failed to confirm the influence of the administration indomethacin on the duration of hospital-

ization.

Group II: The value of testing criterion U=55.5. The critical limits were w (0.01)=41 and w (0.05)=53.

Conclusion: Because U>w (α), we do not reject the null hypothesis; the duration of hospitalization is not affected by the administration of indomethacin. Because the value of the testing criterion is close to a critical limit at a significance level of 0.05, it is possible that once the data are complete the effect of indomethacin could be confirmed.

Group III: The value of testing criterion U=53. The critical limits were w (0.01)=4 and w (0.05)=10.

Conclusion: Because U>w (α), we do not reject the null hypothesis; the duration of hospitalization is not affected by the administration of indomethacin.

During the period in concern, we did not record any complications related to the administration of indomethacin. All of the patients are given prophylactic H2 blockers.

Discussion

Progress has been made over the past 20 years in emergency medicine and intensive care in reducing mortality after severe injuries. Today, SIRS and MODS, the causes of late hospital death after trauma, are important factors influencing post-traumatic morbidity and mortality. Many investigations confirm the importance of the activation of leukocytes with adherence to vascular endothelium and subsequent diapedesis in the pathogenesis of MODS.[2] Serious blunt chest injuries are accompanied with the worsening of ventilation mechanics due to chest and lung injuries as well as with SIRS that always affects the lungs function.[10,14,17] Lung compliance, stroke volume, and cardiac output decrease and pulmonary vascular resistance increases. All the responses are eliminated by indomethacin. Therefore, the development of an injury-induced respiratory failure is multifactorial and timely pharmacological intervention is a suitable addition to treatment, thus improving prognosis in some patients with a serious chest trauma.[10]

If we do not block the onset of the SIRS then the MODS and finally MOF develops. Lethality increases and ranges from 30-80%, according to the number of failed organs. The basic therapy remains artificial pulmonary ventilation with positive end-expiratory pressue (PEEP).[1,20,25] Early institution of partial liquid ventilation proves effective in reducing the alveolar inflammatory response.[3] Partial liquid ventilation is a promising ventilatory strategy for unilateral pulmonary contusion that might ameliorate secondary injury in the contralateral uninjured lung.[13] If ventilatory support strategies fail due to a severe lung or airway injury, extracorporeal veno-venous membrane oxygenation (ECMO) may be an option for the temporary management of gas exchange in trauma patients.[23] Hemofiltration could reduce the plasma levels of some of the mediators of the SIRS.[6]

Epidural analgesia is a preferred method of pain control in patients with severe thoracic trauma without the necessity of mechanical pulmonary ventilation.[5]

Operative chest wall stabilization in flail chest and respiratory insufficiency without pulmonary contusion reduces ventilator time and prevents ventilator-related complications. Patients with pulmonary contusion do not benefit from chest wall stabilization.[18,24]

There is a number of recognized risk factors of mechanical pulmonary ventilation applied as a method of flail chest treatment.[8]

We have had very good experience with Medin plates used for chest wall stabilization in our institution.[11] We applied this method to three patients. As claimed by some other authors, the chest tube insertion was sufficient in the treatment of the majority of patients. Videothoracoscopy was used once for the treatment of a large haemothorax in a cardiopulmonary stable patient. The evacuation of the haemothorax and control of bleeding were carried out in this case. This is the most common indication of videothoracoscopy in a thoracic trauma.[4,12,22]

Spiral CT (contrast enhanced SCT) is much more sensitive and specific in the diagnostics of most thoracic pathologies seen in blunt trauma patients than routine chest X-ray. It should be the first-choice exam in a severe blunt chest trauma. Spiral CT has higher sensitivity in the diagnostics of haemothorax, partial pneumothorax and pulmonary contusion.[16,19,21,22]

Conclusion

Considering the increasing frequency and severity of thoracic injuries and relatively high lethality caused by the injury itself as well as subsequent systemic inflammatory response syndrome, the presented study deals with the possibility of pharmacological blockade of SIRS in affected patients.

The results obtained so far can be summarized as follows: The Group in which indomethacin is administered shows a later increase in inflammatory markers in Groups III and IV and the shorter duration of this increase in Groups II and III. Group III, or rather its subgroup with

indomethacin administration featured a significantly shorter period of mechanical ventilation support.

Six of the seven dead patients in our study belonged to the non-indomethacin subgroup. MOF was the cause of death in two patients in the non-indomethacin subgroup and in one patient in the indomethacin subgroup.

The statistical evaluations completed so far have neither confirmed nor excluded the original hypothesis. The enlargement of the file and the acquisition of further data may lead to a change in the results. Therefore, an assumption may be held that the administration of indomethacin in patients with a blunt thoracic trauma reduces SIRS development and therefore provides a suitable supplement to standard treatment.

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