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ORIGINAL PAPER

Continuous low dose diclofenac sodium infusion to control fever in neurosurgical critical care

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Abstract
Introduction: Aim of this randomized prospective clinical trial is to compare two methods of antipyretics and evaluate their efficacy in controlling fever during the acute phase of brain damage.
Methods: Twenty-two febrile comatose patients: 12 severe traumatic brain injury and 10 subarachnoid hemorrhage divided in 2 groups: Diclofenac low-dose infusion (10 patients) and extemporaneous boluses of NSAIDs (CTRL, 12 patients). The primary outcome measure was length of time with temperature >38°C. Secondary outcome measures were: 1) to assess the effects of each antipyretic strategy on intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP) and heart rate; 2) to monitor adverse effects of each antipyretic strategy. The baseline characteristics in the two treatment groups were similar.
Results: Primary findings: percentage of time per patient with temperature >38°C was significantly lower ($P < 0.0001$) in the DCF group, 4% (0–22%), vs. 34% (8–56%) in CTRL group. In addition, mean T°, max T° were lower in DCF than in CTRL ($P < 0.05$). Secondary findings: CPP and MAP were significantly higher in DCF group ($P < 0.05$) while ICP was not different (NS). However, if ICP pre randomization was < 25 mmHg, CTRL suffered a worst ICP (24 ± 11 vs. 16 ± 7 $P = 0.01$), MAP (89 ± 10 vs. 104 ± 10 $P = 0.01$) and CPP (75 ± 10 vs. 94 ± 17 $P = 0.01$) compared to DCF. No differences between the two treatment were recorded when ICP ≥ 25 mmHg before randomization. There was no gastrointestinal or intracranial bleeding.
Conclusions: Low dose DCF infusion is a potential useful strategy for a successful control temperature better than intermittent NSAIDs dosing, minimizing potentially brain-damaging effects of fever.

Keywords Fever · Antipyretic therapy · Diclofenac sodium · Cerebral perfusion pressure · Intracranial pressure · Traumatic brain injury · Subarachnoid hemorrhage

Introduction

Patients with CNS injury suffer frequently from fever (temperature above 38°C) while in the intensive care unit. Fever actually occurs in 60–90% of acute neurological patients (traumatic brain injury, stroke and subarachnoid hemorrhage) [1–5]. Kilpatrick et al. [5] reported a mean of 4.7 febrile episodes per febrile patient and an average peak temperature of 39.2 ± 0.6°C. Recently, Stocchetti et al [6] showed, in a population of traumatic brain injured patients, that 73% suffered fever.

Extensive experimental and clinical evidence clearly demonstrates that fever has detrimental effects upon morphological evolution and functional outcome of cerebral damage [7–19]. The rationale for treating fever in neurosurgical patients relies mainly upon the prevention of secondary brain injury as, one among many others, that elicited by fever, aiming at better recovery while limiting further damage to the brain. While the possible benefits of mild hypothermia in limiting brain damage are still unproven [20], a meticulous and timely treatment of fever, due to its high incidence and consequences, could potentially benefit a considerable number of patients in ICU.

Nevertheless, the assessment of the risk/benefit ratio of antipyretic therapy requires further clinical experience and

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investigational effort. Antipyretic therapy inherently suppresses the febrile response, whose physiological benefits should not be overlooked. In addition, antipyretic drugs carry specific and predictable side effects. NSAIDs (non-steroidal anti-inflammatory drugs) administration has been reported to cause hypotension (and, as a consequence, reduced CPP), impaired hepatic and renal function, sodium and water retention, and severe oliguria [6, 21–24]. There may be also a theoretical concern for their antiplatelet effects in patients who have bled intracranially for extending the hemorrhage.

Nonetheless, the need for a more aggressive and effective treatment of fever in brain injury patients has been repeatedly advocated [2, 5, 25], even if the optimal method to achieve normal body temperature remains undefined. Failures in antipyretic therapy are indeed common [6, 25, 26], and the management of fever remains often an unsolved problem. Treatment involves the administration of various antipyretic drugs, alone or in combination, such as acetaminophen, ibuprophen, and other NSAIDs, given orally, rectally, or intravenously [27]. Moreover, when it is impossible to manage pyrexia, physical cooling (sponging, cooling blankets, and even direct ice application) is often proposed as a possible alternative [27, 28]. Physical cooling maneuvers, however, require very deep sedation to be effective. Lack of adequate sedation will cause an increased metabolic rate, activation of the autonomic nervous system, and severe thermal discomfort [28–30].

We have been using Diclofenac Sodium (DCF) as the first antipyretic choice in our Department, [31, 32] and we studied the efficacy and safety of low dose DCF continuous i.v. infusion (0.04 mg/kg/h) [33]. We aimed at normal body temperatures while avoiding the major side effects of the full anti-inflammatory i.v. dosage (i.e. DCF 75 mg). The reported study was, however, neither controlled nor randomized, and it was limited to the first 48 h of infusion.

In the present study, an extension of that preliminary report [33], we compared two modes of antipyretics administration: continuous low dose Diclofenac Sodium infusion versus NSAIDs boluses to demonstrate the efficacy of continuous antipyretic therapy for controlling fever during the acute phase of traumatic or vascular brain damage. We also studied intracranial and cerebral perfusion pressure (ICP and CPP) as indicators of the possible more beneficial effects of low dose infusion in cerebral hemodynamics.

Materials and methods

The study was designed as a prospective, randomized, controlled clinical trial and the Ethical Committee of the Monza University Hospital approved it. Informed consent was obtained from each patient's next of kin (comatose patients) as approved by the Institutional Review Board.

Subjects

We screened for possible enrolment of all patients ranging from 14–75 years, admitted to our ICU from April 2000 to June 2001 meeting all the following criteria:

- diagnosis of traumatic brain injury (TBI) or subarachnoid hemorrhage (SAH) (spontaneous rupture of intracranial aneurysm),
- GCS ≤ 8 with at least one pupil reactive after resuscitation,
- presence of fever, defined as bladder temperature ≥ 38°C, developed during the acute phase of cerebral damage, i.e. within 6 days from brain injury,
- monitoring of ICP and CPP.

Patients were excluded if they were pregnant, had suspected hypersensitivity to cyclooxygenase inhibitors and had been enrolled in any other study or when consent was denied. We also excluded patients with advanced renal failure, hepatic failure, severe coagulopathy, active gastrointestinal bleeding, or a life expectancy of less than one day.

Data collection

Demographic and clinical information were obtained and recorded.

Physiological parameters (Bladder temperature (T°), heart rate (HR), invasive mean arterial blood pressure (MAP), ICP, CPP (defined as CPP = MAP-ICP)) were continuously measured and sent to a Windows-based personal computer in order to store data on a minute by minute basis using a software developed by the BrainIT research group (www.brainit.org). Data were screened to exclude outliers values and artifacts.

Arterial and jugular bulb venous blood samples were withdrawn and analyzed at least three times a day, specifically for arterial $paCO_2$ and for oxygen saturation of the bulb of the internal jugular vein ($SjvO_2$).

Laboratory investigations included a daily full blood cell count, coagulation status, plasma electrolytes and concentration of alkaline phosphatase, aspartate aminotransaminase, alanine aminotransaminase, bilirubin, lactate dehydrogenase, and creatinine. Urinary output, urine electrolyte analysis, and fluid balance were recorded daily.

Study interventions

According to their clinical needs, all patients were adequately sedated and mechanically ventilated. They were treated according to the guidelines for management of severe traumatic brain injury [34] and of aneurismal subarachnoid hemorrhage [35].

To detect possible biases in the clinical management of ICP between groups we quantified the intensity of ICP intervention according to a three level scale (list of therapies are not inclusive): (**a**) Standard intensity ICP therapy (sedation, mannitol, CSF drainage, mild hyperventilation ($paCO_2$ 30–35 mmHg)); (**b**) High intensity ICP therapy (induced arterial hypertension, muscle relaxant, moderate hyperventilation ($paCO_2$ 29–25 mmHg)); (**c**) Extreme intensity ICP therapy (barbiturates coma, decompressive craniectomy, severe hyperventilation ($paCO_2 < 25$ mmHg)).

Possible infection sources (e.g. ventilation associated pneumonia (VAP), meningitis, sepsis) were systematically searched for and documented according to the definitions of the Center for Disease Control [36].

Randomization groups and study design

Patients were randomized when bladder temperature had been higher than 38°C for at least 30 min or immediately when temperature was higher than 39°C. A 2-group design was used: Group 1) DCF group - low doses Diclofenac Sodium infusion ($n = 10$) and Group 2) CTRL group - i.v. NSAIDs boluses ($n = 12$). Patients were assigned to the study groups in a blinded fashion with the use of a simple (independent) random sample.

Group 1: low doses diclofenac sodium infusion (DCF group)

Following a loading DCF i.v. bolus (0.2 mg/kg diluted in 100 ml normal saline [32] over 30 min), a continuous infusion of DCF (75 mg in 50 ml normal saline) was started. Infusion dosage (0.004–0.08 mg/kg/h) was titrated according to antipyretic patient response. The goal of the titration algorithm was to reach and maintain an internal temperature lower than 37.8°C by the lowest effective infusion. When temperature had reached the target range, we attempted, at least at any shift, to decrease of about 0.15 mg/h (0.002 mg/kg/h) the infusion rate. The DCF infusion was stopped when temperature had been lower than 38°C for at least 12 h and the infusion had been running at the minimum rate (0.004 mg/kg/h).

Group 2: Control (CTRL, NSAID group)

Fever was treated by extemporaneous antipyretic (one of the following NSAIDs chosen by the attending physician: DCF, ketoprofene and proparacetamol). If the patient remained febrile, the minimum interval between boluses administration was at least 4 h. Bolus dose was 0.2 mg/kg for DCF [32], 100 mg for ketoprofene, and 1000 mg for proparacetamol. All boluses were diluted in 100 ml normal saline and infused over 30 min.

Antipyretics administration was suspended when temperature remained lower than 38°C for at least 12 h.

We divided the study in three periods: Baseline (values 30 min before randomization), treatment (days of intense fever treatment-range 3–10 days), and post treatment (24 h following the stop of antipyretic therapy)

Primary outcome measures

Fever control was quantified by the ratio between the length of time during which temperature was higher than 38°C and total treatment time.

Secondary outcome measures

We assessed the effects of the antipyretic strategy upon selected cerebral and systemic parameters (ICP, CPP, MAP and HR). We defined the time during which the secondary insult was present as the time during which CPP was ≤ 70 mmHg and/or ICP was ≥ 20 mmHg. The ratio secondary insult time/total treatment time was then computed.

Following the comparison between groups, we performed a separate analysis to better evaluate the effect of fever upon cerebral hemodynamics. We analyzed patients whose pre-randomization (12 h before starting treatment) ICP was ≥25 mmHg for at least 15 min (N. 10) separately from those whose pre-randomization ICP was always lower than 25 mmHg (N. 12). The latter subgroup was supposed to be still amenable to ICP increases related to high temperature, while in patients in whom ICP was already high (first subgroup) this major pathophysiological derangement could overshadow any possible additional effect of fever.

To monitor the possible adverse effects of each antipyretic strategy we surveyed and recorded all described laboratory variables, follow up CT scans (performed during treatment and post-treatment periods) for evidence of any new or enlarging intracranial hemorrhagic lesions, as well as any allergic reaction. Every patient was tested for occult blood in the stool and/or stomach.

Neurological outcome was assessed according to the Glasgow Outcome Scale (GOS) six months after brain injury. We grouped patients in a simplified two-category GOS: Unfavorable outcome (death, severe disability, persistent vegetative state) and Favorable outcome (good result and moderate disability) [20].

Statistical analysis

Statistical analysis was performed with the Data Desk software package (DataDesk 6–Data Description, Inc.

Ithaca, NY). Data are presented as means SD or as median when they were not normally distributed. They were compared by using the Mann–Whitney U test, when to account for non-Gaussian distributions, or with analysis of variance when data were normally distributed. The chi-square test, or the Fisher exact test when required, was used to analyze differences in frequency among groups.

Based on an expected DCF treatment-related relative reduction of 70% (from 35% with NSAIDs to 10% with DCF) in the length of time during which temperature was higher than 38°C and a power of 0.90 and a significance level of 0.03, we planned a sample size of 30 patients (15 + 15). On the basis of an interim analysis demonstrating that the expected treatment effect (primary outcome) was attained with a lower sample size, enrolment was stopped at 22 patients. According to the fact that clinical trials that stop early are prone to exaggerate the magnitude of treatment effect, we set an extreme significance level ($P < 0.01$) for early stopping, on the basis that the overall type 1 error will not be greatly influenced [37].

Results

Twenty-two patients were randomized: 12 (55%) had TBI and 10 (45%) SAH. At the time of enrolment the baseline characteristics of the patients in the two treatment groups were similar (NS), even if a trend of younger age has been recorded in treated population (Table 1).

The median time from injury to randomization was 65 h in the DCF group and 54 h in the CTRL group (NS). At randomization, median bladder temperatures were similar between groups (respectively 38.3 °C vs. 38°C–NS), as were systemic and cerebral parameters (Table 2).

Fever control (Primary end-point)

Fever treatment was maintained for 6.6 ± 2.3 days in the DCF group and for 5.9 ± 1.9 days in the CRTL group (NS), for a total of 197280 monitored minutes (sum of minutes recorded: 95040 min for DCF and 102240 for CTRL group). Mean recording time per patients in the two groups was not different.

The percentage of time per patient with temperature above 38°C (vs. total treatment time) was significantly lower in DCF group: 4% (range: 0–22%) of time in DCF versus 34% (range: 8–56%) of time in CTRL group ($P = 0.0003$). The mean core temperature during treatment was 37.3 ± 0.2°C in the DCF group, which was significantly lower than CTRL mean temperature (37.6 ± 0.3°C; $P = 0.006$). The maximum temperatures recorded during the treatment period were significantly different: 37.8 ± 0.2°C versus 38.5 ± 0.4°C respectively in the DCF and CTRL group ($P < 0.0001$). Minutes per day with fever were significantly less in DCF group than in CTRL group (Fig. 1).

The average DCF infusion dosage was 0.03 ± 0.02 mg/kg/h. The total amount of DCF administered by infusion to the whole group was 2496 mg. In the CTRL group, NSAIDs were administered 129 times to control fever for a total of 1086 mg of DCF as i.v. boluses (tot 78 boluses)

Table 1 Characteristics of the patients in the CTRL and DCF treatment groups at the time of enrolment. The baseline characteristics of the patients in the two treatment groups were similar (NS)

CTRL Group	DCF Group	Significance	
Patients	12 (55%)	10 (45%)	NS
Age (years)	54 ± 17	40 ± 18	NS
Sex (male)	6 (67%)	8 (60%)	NS
Pathology (TBI %)	6 (50%)	6 (60%)	NS
GCS motor component (median)	5	5	NS
Pathologic pupils	2 (17%)	2 (20%)	NS
SAH			
WFNS (median)	4	4	NS
Focal Motor deficit	2 (33%)	2 (50%)	NS
CT scan:			
Intracranial Haematoma	2 (33%)	3 (75%)	NS
Volume (% >25 ml)	2 (33%)	2 (50%)	NS
Ischemia	2 (33%)	3 (75%)	NS
Traumatic brain injury (TBI)			
GCS motor component (median)	5	5	NS
CT scan:			
EDH	2 (33%)	1 (17%)	NS
SDH	3 (50%)	3 (50%)	NS
ICH	1 (17%)	3 (33%)	NS
Volume (% >25 ml)	5 (83%)	3 (50%)	NS
Shift (5 mm)	4 (67%)	3 (50%)	NS
GOS (Favorable outcome)	10(83%)	7(70%)	NS

TBI = Traumatic brain injury

GCS = Glasgow coma scale

Pathologic pupils = Fixed and dilated or anisocoric pupils

SAH = Aneurysmal subarachnoid hemorrhage

WFNS = Grading scale for subarachnoid hemorrhage developed by the World Federation of Neurological Surgeon.

CT scan (first CT scan or the worst CT scan obtained before randomization)

EDH = Epidural hematoma

SDH = Subdural hematoma

ICH = Intracerebral hematoma and cerebral contusion

Shift = Midline shift in millimeters

GOS = Glasgow Outcome Scale. We grouped patients in a simplified two-category GOS: Unfavorable outcome (death, severe disability, persistent vegetative state) and Favorable outcome (good result and moderate disability) (20).

Table 2 Systemic and cerebral median parameters at randomization (baseline values = data obtained during the 30 min before randomization)

Variable	DCF group	CTRL group	p.
Median MAP (mmHg)	86	85	0.5
Median ICP (mmHg)	17	13.5	0.09
Median CPP (mmHg)	71	72	0.6
Median $SjvO_2$ (%)	67.2	71.5	0.4

MAP = Invasive mean arterial pressure

ICP = Intracranial pressure

CPP = Cerebral perfusion pressure (MAP-ICP)

$SjvO_2$ = oxygen saturation of the bulb of the internal jugular vein

plus a total of 14,000 mg of proparacetamol (tot 14 i.v. boluses) and a total of 3700 mg of ketoprofene (tot 37 i.v. boluses).

Cerebral and systemic hemodynamics

During fever management, CRTL group MAP and CPP were lower than in DCF group (Table 3). Mean intracranial pressure, HR and $SjvO_2$ did not differ significantly between the two treatment groups (Table 3). Throughout the treatment time, the median proportion of time during which ICP was ≥ 20 mmHg (DCF: 15% vs. CTRL: 17%; NS) or CPP was ≤ 70 mmHg (DCF: 16% vs. CTRL: 36%; NS) were not different between the two groups.

Next, we analyzed separately patients with pre-randomization ICP lower than 25 mmHg (N. 12: ICP 15.57.1 mmHg, range 4–24) and those with ICP ≥ 25 mmHg (N. 10: ICP 36.411.1 mmHg, range 25–54).

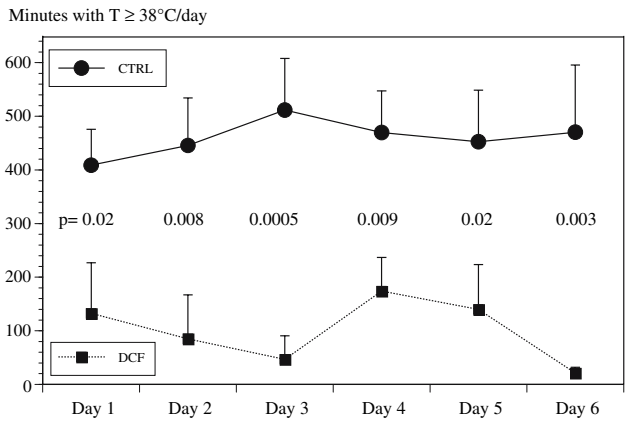

Fig. 1 Minutes per day with a temperature≥38°C in the DCF and CTRL groups during the first six days of fever control period. Minutes with fever are significantly lower in DCF group than in CTRL for any day considered. *P* values are for the comparison between the groups at any different days of the treatment period

Table 3 Cerebral and systemic parameters in the two groups of fever treatment during intensive fever management

Variable	DCF group	CTRL group	*P*
Mean ICP (mmHg)	15.7 ± 6.6	14.3 ± 5.4	0.1
Mean CPP (mmHg)	79 ± 16	74 ± 11	0.03
Mean MAP (mmHg)	95 ± 12	90 ± 11	0.009
Mean HR (bpm)	90 ± 14	86 ± 15	0.1
Mean $SjvO_2$ (%)	70 ± 8	69 ± 4	0.4

MAP = Invasive mean arterial pressure

ICP = Intracranial pressure

CPP = Cerebral perfusion pressure (MAP-ICP)

HR = Heart rate

$SjvO_2$ = Oxygen saturation of the bulb of the internal jugular vein

No evident effect of the treatments on ICP, CPP and MAP was detected in the high (≥ 25 mmHg) pre randomization ICP group, while the effects of treatment were significant in the subgroup of patients with low pre randomization ICP (lower than 25 mmHg). In this subgroup indeed ICP was higher, CPP and MAP lower in CTRL than in patients treated with DCF infusion (Table 4). Moreover, the incidence of ICP ≥ 20 mmHg per patient more than once was higher in CTRL than in DCF group: respectively 67.5% and 33.5% ($P \leq 0.01$) during fever treatment.

CTRL and DCF groups had similar ICP therapy intensity levels, vasopressor requirements to maintain CPP and sedation. More furosemide was administered in CTRL group (44 ± 40 mg/die in CTRL vs. 17 ± 10 mg/die in DCF; $P = 0.02$) to achieve a daily urinary output comparable to the one of the DCF group (3940 ± 1307 vs. 3690 ± 1307 ml; NS).

POST treatment data

No difference was found in any of the evaluated parameters (temperature, minutes with temperature ≥ 38°C, MAP, ICP, CPP, HR, $SjvO_2$) between groups after stopping antipyretic therapy. Likewise, no differences were noted between the two groups for all blood tests performed after treatment time.

Complications, infections and outcome

All blood and urine tests and urinary volume were measured serially over the study period to evaluate the effects of the treatment on renal and hepatic function; no significant differences were detected between the groups.

Infection was clinically suspected in all patients and they were treated with antibiotics. White cells counts were higher than 10,000/mm^3 but not significantly different in

Table 4 Treatment period: Maximum ICP, mean CPP and mean MAP in Control and DCF groups when ICP pre-randomization was above or less than 25 mmHg. There were statistically significant differences between the groups for any of the parameters explored when ICP pre-randomization was 25 mmHg

	ICP CTRL	ICP DCF	CPP CTRL	CPP DCF	MAP CTRL	MAP DCF
Pre-randomization ICP ≥ 25 mmHg	30.5 ± 13.1 mmHg	33.8 ± 13.2 mmHg	72 ± 11.3 mmHg	73.6 ± 11.8 mmHg	92.2 ± 10.5 mmHg	91.3 ± 10.1 mmHg
Significance	NS		NS		NS	
Pre-randomization ICP < 25 mmHg	24 ± 11.8 mmHg	16 ± 7.4 mmHg	75 ± 10.2 mmHg	94.2 ± 17 mmHg	89.5 ± 10.6 mmHg	104.3 ± 10.5 mmHg
Significance	$P = 0.01$		$P < 0.0001$		$P < 0.0001$	

the two groups. On a total of 26 infections diagnosed (11 in DCF and 15 in CTRL group) the predominant site of infection was the lung: 19 patients had ventilator associated pneumonia, 2 meningitis (patients with cerebral spinal fluid (CSF) fistulae), and 4 were affected by other infections. All were not significantly different in the two groups.

Gastrointestinal (occult blood in the stomach and/or stool) and intracranial bleeding (at follow up CT scan during the treatment and post-treatment periods) or allergic reactions were never observed.

Mortality at 6 months did not differ significantly in the DCF and CTRL groups. There were no differences between the DCF and CRTL groups in favorable outcome (dichotomized GOS): 70% of the patients in DCF and 83% in CTRL group (NS) (Table 1).

Discussion

The current study, planned on our previous observational work [33], demonstrates that, in patients with acute brain damage, DCF continuous infusion effectively reduces fever and contributes to minimize secondary cerebral insults by stabilizing hemodynamic and cerebral parameters. Diclofenac is an inhibitor of cyclooxygenase and it has analgesic, anti-pyretic, and anti-inflammatory activities. Its intravenous administration has been previously reported [32, 38–40] and it was chosen for this trial because previous studies in humans showed that it has a good antipyretic effect even at very low doses [32, 33]. The primary end-point of this study was to provide a more steady and titrable control over fever by a continuous infusion than intermittent dosing, minimizing its potentially brain damaging effects. The mean and maximum bladder temperature during treatment in the DCF group was significantly lower than CTRL temperature. Body temperature has been shown to be a very strong prognostic predictor in patients with brain injury. For a single centigrade increase in body temperature the poor outcome risk in ischemic stroke patients increases 2.2 times; the earlier the increase in temperature, the stronger the relationship between brain damage and increased temperature [1]. We started our treatment in the acute phase of injury when the brain susceptibility to secondary insults is still a central problem.

Temperature is controlled poorly in current practice, despite the use of antibiotic and antipyretic therapy. The attention paid to the fever problem in our ICU and the use of Diclofenac as the drug of choice in fever treatment, seems to compare favorably with other reported methods [2, 5, 6, 11, 25, 26]. Actually, they were successful in controlling fever in about less than half of patients. Moreover, we recorded fever and other physiological parameters on a continuous basis and this strengthen our results but make comparison with other trials, where usually only few measure per day were attained, very complicated. Moreover, it is important to remark that our results showed that fever treatment is better accomplished, not unexpectedly, using a continuous infusion strategy rather a waiting extemporaneous prescriptions.

It was somehow difficult to compare the total amount of antipyretic drugs used in the 2 treatment groups. It seems anyhow that patients in DCF group required lower doses of antipyretic drugs. However, if DCF infusion was decreased too rapidly, because of an apparently good therapeutic effect, it often resulted in temperature rebound.

Anti-inflammatory drugs may have an effect on hemodynamics [6, 21–24] and care must be taken to avoid hypotension, and consequently CPP decrease, when using these agents. In DCF group we got a better stability of hemodynamic and cerebral parameters. The power of our study to detect a significant change in these parameters may have been limited by the small number of patients studied. In part, our failure to show a clear ICP difference between the two groups comes from the undue optimism that a single agent could reverse most, if not all, of the events cascade occurring after brain damage. Likewise, we would like to suggest the confounding effect of the challenging intracranial hypertension as a direct consequence of trauma on our measures. It may mask the additional detrimental cerebral effect of fever in the two populations. The analysis of ICP, CPP and MAP in the population with a normal ICP at randomization, rather than in the entire

population, was performed to obtain a more sensitive evaluation of the effect of therapy on injury evolution. In patients with ICP pre randomization < 25 mmHg, a subgroup supposed to be still susceptible to ICP worsening related to temperature, we noticed that CTRL therapy attained a higher ICP and lower CPP and MAP, both negatively influenced by NSAID administration (Table 4). By contrast in the same subgroup, DCF infusion attained the best results in ICP control and hemodynamic stability.

Evaluation of hepatic, renal function and hemorrhagic events failed to demonstrate adverse effects when Diclofenac was administered continuously early in the course of cerebral damage.

Notwithstanding the fever suppression in the DCF group, the incidence of infections and sepsis did not increase.

We found no significant effect of any of the two treatment modalities on outcome. However, the effect, if any, which fever treatment has on the functional outcome of critically ill neurosurgical patients is still under debate.

Conclusion

Fever control in brain-injured patients may be a very important intervention and currently practiced methods are not uniformly successful. This study validated a symptomatic therapy to control fever in patients with acute brain damage and as a result to limit any possible secondary insults to the brain related to fever. Low dose DCF infusion showed a marked and enduring reduction in body temperature. It provides a potential tool for the intensivist to successfully and flexibly control temperature better than intermittent dosing, minimizing fever potentially brain damaging effects.

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